UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS

CHILDREN'S HEALTH DEFENSE, DEBORAH L. ELSE, an individual, and SACHA DIETRICH, an individual, Plaintiffs, v. FOOD & DRUG ADMINISTRATION, and JANET WOODCOCK, acting commissioner of Food & Drugs, Defendants.	**Case No. 6:22-cv-93** **COMPLAINT**

INTRODUCTION

The greatest threat to a government is often itself. The most dangerous tool of government is emergency power. This case concerns the misuse of that power by Defendant Food & Drug Administration ("FDA"). By claiming emergency powers, the FDA eliminated the notice-and-comment process, ignored citizen petitions, abandoned traditional safety mechanisms for assessing drugs injected into interstate commerce, ignored express legislative limits on their actions, and now claim to be beyond judicial review. Defendants used this precarious emergency power to push dangerous drugs on minors, mislabel and misbrand those drugs to the public, knowing their mislabeling would lead these mislabeled drugs to be mandated on children as young as 5 years old.

SUMMARY

1. Under the pretext of Emergency Use Authorization powers (two years into this "emergency"), Defendant FDA authorized a dangerous drug for minor children as young as 5 years old to address COVID-19, which poses less risk to a 5-year-old than the ordinary flu. The FDA, using its emergency powers, redefined this drug as a "vaccine" even though it did not meet the century-long definition of the term, leading to the broadening of the definition of "vaccine" to include this new experimental biologic. The FDA failed to provide for any notice-and-comment period, failed to provide for any citizen petition recognition nor redress of petitioner concerns and grievances, claimed these emergency powers provided for no legislative limit beyond their expansive claims, and even claimed these emergency powers prevent and preclude judicial review by citizens. The FDA has become an agency that declares its own law, enforces its own law, and adjudicates its own law, with children now the sacrificial lamb to this precarious power grab.

2. As an agency founded on regulating interstate labeling of products (not as a supervisory medical or scientific agency), the core of the Defendants' work is making sure the marketing of drugs conform to their known qualities, especially highlighting the drug's risks, the limits on the drug's proven efficacy, and conforming the marketing of any drug to the requirements of informed consent, the universal governing medical norm and *jus cogens* principle governing all civilized societies, as codified in the Nuremberg Code of 1947. Instead, the FDA shirked their purpose and rushed an untested product to market, mislabeled this experimental gene therapy a "vaccine", and allowed it to be mandated upon minors without their informed consent.

3. The FDA ignored, violated, and discarded their own laws and rules limiting the marketing of drugs, and pushed this drug onto minor children with false and manipulative advertising, even stooping so law as to use the popular children's program Sesame Street, and the children's favorite character, Big Bird to promote this mislabeled product.

4. The FDA's unchecked and unbridled reign over COVID-19 pharmaceuticals is the foundation of all vaccination policies and mandates in the United States today. The FDA determines which drugs can be mandated because it's authorization, approval and labeling is the first foundational centerpiece of any drug being mandated in the first place. Children now face loss of access to needed transplants, medical care, educational programs, travel, and even basic participation in public life based on the FDA's actions.

PARTIES

5. Plaintiff CHD is a not-for-profit membership organization incorporated under the laws of Georgia. Plaintiff sues in its own capacity and on behalf of its constituent members who have been affected by Defendants' actions. FDA's conduct toward children, including misuse of emergency powers to authorize the drug, then the public marketing and mislabeling of the drug to minor children as young as 5 years old, caused a serious diversion of the organization's resources from its original mission in public education and protection of children to correct this critical error and try to protect the members and mission of CHD from Defendants' illicit actions and ill effects thereof. Additionally, CHD was denied its right to petition, the chance at notice-and-comment, and its procedural remedies under the Administrative Procedures Act because of the FDA's misuse of its emergency powers rather than following the proper protocol for biologic licenses for children.

6. Plaintiff Deborah L. Else is a member of CHD and a resident of Bell County, Texas. She is a long-time pharmacist and the parent of R.E., a 10-year-old student at Thomas Arnold Elementary School in Salado, Texas. Her child is at imminent risk of immediate harm from FDA's action to authorize Pfizer's COVID-19 biologic for children aged 5-11, and her child is in the class the Defendant agencies targeted with their unlawful authorization and illicit marketing of this drug.

7. Plaintiff Sacha Dietrich is a resident of Bell County, Texas. She is the parent of H.D. and K.D., who are 11 and 7 years old, respectively. Her children are at imminent risk of immediate harm from this Emergency Use Authorization (EUA) biologic, including but not limited to coercion and pressure to receive the biologic, local and school mandates, and severe adverse reactions should they receive the drug, and her child is in the class the Defendant agencies targeted with their unlawful authorization and illicit marketing of this drug.

8. Defendant FDA is an agency within the U.S. Department of Health and Human Services. The FDA is primarily a labeling and marketing agency, "responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines, and other biological products."[1]

9. Defendant Janet Woodcock is sued in her official capacity as Acting FDA Commissioner.

JURISDICTION AND VENUE

10. This action arises out of Defendants' misuse of emergency powers under 21 U.S.C. § 360bbb-3, and their non-compliance with the Administrative Procedures Act, 5 U.S.C. §

[1] *FDA Fundamentals,* U.S. Food & Drug Administration, available at https://www.fda.gov/about-fda/fda-basics/fda-fundamentals.

500 *et seq*.

11. This lawsuit raises federal questions over which this Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1361.

12. Pursuant to 28 U.S.C. § 1391(e), venue is proper in the Western District of Texas, where Plaintiffs Deborah L. Else and Sacha Dietrich reside. Under 5 U.S.C. § 703, venue is proper in any court of competent jurisdiction.

13. An actual and justiciable controversy exists between Plaintiffs and Defendants. Plaintiffs are in the class directly injured by this illicit marketing of this drug to minor children, and Plaintiff organization must, and has, diverted substantial resources due to it.

STATEMENT OF FACTS

14. We face an unparalleled moment in the history of the FDA and public health: the race to rush a vaccine authorization for very young minor children without adequate clinical trials, without consideration of relevant information, without robust debate, and without even meaningful public participation in the citizen petition process. The FDA's extraordinary emergency authorization for young, minor children aged 5-11, who face less risk from COVID-19 than from the seasonal flu, endangers their safety, as these biologics lack good manufacturing policies, lack strict safety safeguards, lack liability accountability, and indeed do not even fit the traditional definition of "vaccine."

15. This biologic uses experimental technology to combat a novel virus from a viral family with no history of vaccine success and attempts to attack a virus that continues to mutate in ways prior vaccine studies did not even address. This unwarranted authorization endangers vaccine confidence, as it follows a historic path littered with disastrous debacles of unsafe

yet sanctioned drugs and biologics that have devastated confidence in public health generally.

16. On October 29, 2021, the FDA granted an Emergency Use Authorization (EUA) for Pfizer-BioNTech's COVID-19 biologic for children ages 5-11, even though this product poses imminent risk to that portion of the population without proportionate benefit.

17. To justify the authorization, the FDA ignored, and even hid, data showing severe short-term risks of COVID-19 vaccination for children and never admitted that the agency's abbreviated studies couldn't have been long enough in duration to assess long-term severe and irreversible injury. The FDA could not, and did not, arrive at a reasoned explanation of whether benefits outweigh the risk of injury for children aged 5-11. The small-cohort clinical trials, too short to render meaningful data, are still in the process of being conducted. If this dangerous rollout is allowed to continue, there are certain to be untold casualties and injuries. Children, expected to have the greatest number of years of life ahead of them, run the greatest risk of vaccine injury, yet have the lowest risk from COVID-19 itself than any other age group.

18. In this, the latest in a series of premature approvals and authorizations, Defendants have abused their emergency powers, denied CHD its procedural right to seek redress via citizen petition, redefined the term "vaccine" in violation of procedural due process, failed to satisfactorily articulate standards for assessing the safety, efficacy, and necessity for the vaccine, and promoted the fraudulent marketing of a drug targeted at children, in violation of the Administrative Procedures Act ("APA"). Furthermore, the FDA failed to perform the function for which the agency was intended: address the health and safety concerns regarding drugs administered to the American public.

FDA's Grant of Emergency Use Authorization for Children Ages 5-11

19. On January 31, 2020, Alex M. Azar, II, the Secretary of Health and Human Services, declared the existence of a public health emergency pursuant to § 319 of the Public Health Service Act, 42 U.S.C. § 247d *et seq*. Shortly after, on March 13, 2020, President Trump declared a national emergency.

20. Section 564 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 360bbb-3, authorizes the FDA to issue an EUA for a biologic under certain emergency circumstances, allowing a product to be introduced and administered to the public even when it has not gone through the review process necessary for approval and licensure.

21. In such an emergency, the Secretary of Health and Human Services may issue EUAs if he concludes that the following facts exist: (1) a serious or life-threatening disease is present; (2) a product "may be effective" in treating or preventing it; (3) there is"no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition;" (4) a risk-benefit analysis that measures both the known and potential benefits of the product against the known and potential risks of the product is positive; and (5) that the patient's option to accept or decline the product is protected through informed consent. 21 U.S.C. § 360bbb-3(c)(1)-(5).

22. On October 29, 2021, the FDA abused its discretion under the emergency use statute and recklessly granted Emergency Use Authorization for a pediatric Pfizer-BioNTech COVID-19 vaccine for 5- through 11-year-olds.

23. On October 26, 2021, the FDA held a Vaccines and Related Biological Products Advisory Committee ("VRBPAC") meeting to discuss Pfizer's request to amend its EUA to

allow for the use of the Pfizer-BioNTech COVID-19 vaccine in children ages 5-11 (Exh. 4).[2]

Inadequacy of Clinical Trials

24. FDA's press release (Exh. 1) announcing authorization of Pfizer-BioNTech for 5- through 11-year-olds noted that the authorization was based on a trial that included, "approximately 3,100 children aged 5 through 11 who received the vaccine," and concluded that "no serious side effects have been detected in the ongoing study."[3] The press release went on to state, "The Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age is administered as a two-dose primary series, 3 weeks apart, but is a lower dose (10 micrograms) than that used for individuals 12 years of age and older (30 micrograms)."

25. Although Defendant Janet Woodcock, the acting commissioner of FDA, did not sign the press release, she still bears responsibility for the FDA's actions as pleaded herein.

26. The clinical trials performed to test safety and efficacy of the COVID-19 biologics were woefully inadequate and rife with fraudulent error that nullifies the reliability of the results.

27. Since the Defendant agency's first issuance of an EUA for Pfizer-BioNTech COVID-19 vaccine for individuals 16 years of age and older on December 11, 2020, the FDA has continued to issue EUAs to Pfizer even though its Phase III clinical trials remain, at the time of this filing, incomplete. Pfizer's clinical trial Estimated Primary Completion Date is

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[2] *Vaccines and Related Biological Products Advisory Committee October 26, 2021 Meeting Announcement,* FDA (October 26, 2021), available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-26-2021-meeting-announcement.

[3] *FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age*, available at https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age.

November 2, 2022, and the Estimated Study Completion Date is May 2, 2023.[4]

28. The few clinical trials that have been conducted are untrustworthy and riddled with error. On November 2, 2021, the British Medical Journal published alarming information brought forward by whistleblower Brook Jackson, a regional director at the Ventavia Research Group, regarding Pfizer's Phase III clinical trial for the COVID-19 vaccine. Ventavia Research Group is a privately owned clinical research company in Texas responsible for completing a portion of the clinical research upon which Pfizer, the FDA, and the public, based their faith on the safety and efficacy of COVID-19 vaccines. Jackson conveyed that "the company falsified data, unblinded patients, employed inadequately trained vaccinators, and was slow to follow up on adverse events reported in Pfizer's pivotal phase II trial." Jackson expressed her concerns regarding "poor laboratory management, patient safety concerns, and data integrity issues" to her supervisors at Ventavia, to no avail. Documentation gathered by Jackson demonstrates that these problems have been continuously occurring since shortly after the clinical trial began. When Jackson was unsuccessful in submitting her concerns to Ventavia, she called and emailed a written complaint to Defendant FDA on September 25, 2020 regarding the unsound practices she had witnessed. That same day, Jackson was fired from Ventavia.[5]

29. The email sent to the FDA documents a number of concerning practices Jackson had witnessed: "participants placed in a hallway after injection and not being monitored by clinical staff;" "lack of timely follow-up of patients who experienced adverse events;"

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[4] *See Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT04368728.

[5] Paul Thacker, *Covid-19: Researcher Blows the Whistle on Data Integrity Issues in Pfizer's Vaccine Trial,* available at https://www.bmj.com/content/375/bmj.n2635.full.print.

"protocol deviations not being reported;" "vaccines not being stored at proper temperatures;" "mislabeled laboratory specimens;" and "targeting of Ventavia staff for reporting these types of problems."[6] Although the FDA responded to her email, the agency failed to follow up or inspect Ventavia after the complaint was made.[7]

30. A former Ventavia employee expressed that the FDA "rarely does anything other than inspect paperwork, usually months after a trial has ended."[8] Indeed, a 2007 Department of Health and Human Services report found that "the FDA inspected only 1% of clinical trial sites" and "inspections carried out by the FDA's vaccines and biologics branch have been decreasing in recent years, with just 50 conducted in the 2020 fiscal year."[9]

31. In the FDA advisory committee meeting held on December 10, 2020, to discuss Pfizer's first application for EUA for its COVID-19 vaccine, Pfizer failed to mention any problems at the Ventavia site. Indeed, the FDA admits in its published summary of inspections of Pfizer's clinical trials that only nine of the trial's 153 sites were inspected; Ventavia was not one of them. "Since Jackson reported problems with Ventavia to the FDA in September 2020, Pfizer has hired Ventavia as a research subcontractor on four other vaccine clinical trials."[10]

32. Furthermore, the FDA did not conduct *any* clinical trials that properly tested the altered formula administered to children. As was stated during the VRBPAC October 26, 2021 meeting, the stabilizer used in the biologic during the trials is different from what was authorized. While manufacturers have claimed that safety studies continue and that they are

[6] *Ibid.*
[7] *Ibid.*
[8] *Ibid.*
[9] *Ibid.*
[10] *Ibid.*

still following subjects for long-term safety, the absence of any control group makes that claim risible.

33. The FDA stopped short of citing adequate data—only promising future follow-up: "Our comprehensive and rigorous evaluation of the data pertaining to the vaccine's safety and effectiveness should help assure parents and guardians that this vaccine meets our high standards," stated Acting FDA Commissioner Janet Woodcock, M.D.[11]

34. This hauntingly echoes the FDA's confirmation in its August 23, 2021 EUA reissuance that vaccine safety and efficacy for the 12-year-old through 15-year-old age group had not been established.[12] The FDA's memorandum for extension to 12- through 15-year-olds acknowledges "unknown benefits and data gaps" in "duration of protection," "effectiveness in certain populations at high risk of severe COVID-19," "effectiveness in individuals previously infected with SARS-CoV-2," "vaccine effectiveness against asymptomatic infection," "vaccine effectiveness against mortality," and "vaccine effects against transmission," proving that almost nothing is actually known about the benefits of the Pfizer biologic in the 12- through 15-year-old age group.[13]

35. The World Health Organization expressed a similar sentiment in July 2021: "More evidence is needed on the use of the different COVID-19 vaccines in children to be able to

[11] *FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age*, available at https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age.
[12] *Letter of Authorization (Reissued)*, U.S. Food & Drug Administration, August 23, 2021.
[13] *Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum,* U.S. Food & Drug Administration, available at https://www.fda.gov/media/148542/download.

make general recommendations on vaccinating children against COVID-19."[14]

36. Furthermore, Pfizer willfully ignored health concerns raised by clinical trials not directly testing the cohort at issue and failed to investigate further prior to authorization. A Pfizer clinical trial found that the mRNA dosage of the Pfizer vaccine has caused severe fevers in younger children.[15] The clinical trial found that children ages2-5 who received 10 micrograms of mRNA experiences fevers that were both more common and more severe than those other age cohorts.[16] As a result, Pfizer opted to lower the dosage in future tests from 10 micrograms to 3 micrograms for children aged 2-5, for which the vaccine is not yet authorized.[17] However, the same 10-microgram dosage is administered to and authorized for children ages 5-12, with no adjustment for weight. 5-year-olds receive the same dosage that causes severe fevers in children ages 3-4, although the size and robustness of many 5-year-olds is not significantly different than children a year or two younger.

37. Despite this, Defendants have continued to recklessly and heedlessly push this drug on innocent Children. On January 3, 2022, the FDA authorized a third Pfizer booster shot for children ages 12-15 without going through the proper authorization process. On January 18, 2022, GOP lawmakers drafted a letter to the FDA and Acting Commissioner Janet Woodcock in response, questioning why the agency did not rely on its typical committee

[14] *COVID-19 Advice for the Public: Getting Vaccinated*, World Health Organization (Nov. 15, 2021), available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice.
[15] *Analyst and Investor Call to Discuss the First COVID-19 Comprehensive Approach: Pfizer-BioNTech Vaccine and Pfizer's Novel Oral Antiviral Treatment Candidate,* Pfizer, December 17, 2021, available at Presentation Title (q4cdn.com).
[16] *Id.*
[17] *Pfizer and BioNTech Provide Update on Ongoing Studies of COVID-19 Vaccine,* Pfizer (December 17, 2021), available at https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-ongoing-studies-covid-19.

approval process prior to authorizing a third Pfizer shot for children ages 12-15.[18] More than two dozen members of the House and Senate signed the letter demanding an explanation for why the FDA decided to forego consultation with the Vaccines and Related Biological Product Advisory Committee (VRBPAC) prior to issuing authorization. As of the time of this filing, Defendants have failed to respond or provide an explanation for the omission.

38. Plaintiffs are therefore justifiably concerned of the untold risks that this experimental injection may pose for children in the 5-11 age group due to the inadequacy of the clinical trials and Defendants' insufficient guarantee of safety.

Approving Drugs and Biologics: Citizen Participation

39. CHD filed a Citizen Petition with the FDA (Exh. 2) on May 16, 2021, asking the FDA to refrain from licensing COVID-19 vaccines and to revoke EUAs for the three existing COVID-19 vaccines. Individuals have submitted over 30,000 comments on this petition.

40. Despite a dismissive and unsatisfactory response on August 23, 2021 (Exh. 3), the same day the agency approved the Pfizer "Comirnaty" biologic, the FDA has done nothing to assuage the public concerns outlined in the Citizen Petition. Rather, the FDA has forged ahead on its path to inject this experimental drug into every American's arm.

41. Nothing destroys public confidence in vaccines more than rushing their authorization and approval without addressing public concerns and without the regulatory agencies explaining the standards, if any, used for authorization, approval, and licensure.

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[18] *GOP Lawmakers Ask FDA for Answers in Pfizer COVID-19 Booster Approval Process for Children: 'Quite Troubling,'* Fox News, January 19, 2022, available at https://www.foxnews.com/politics/gop-lawmakers-fda-answers-pfizer-booster-children.

42. The FDA Citizen Petition process is meant to prevent this from happening. Citizen participation, through a Citizen Petition, confers some democratic participation in the drug or biologic approval process, provides for the kind of free discussion and public engagement that imposes the scientific method on the process, and engenders public confidence in the vaccine itself. If you cannot trust the process, you cannot trust the result of that process. A study in May 2021 showed that roughly half the U.S. population does not trust the FDA, CDC, or other major public health organization; this percentage is guaranteed to be higher now. If more than half of the population is unprepared to trust the FDA's results and recommendations, the relevance of the Citizen Petition process cannot be understated.

43. Defendant has denied Plaintiffs their procedural right to participate in the notice and comment process or answers to their concerns in the Citizen Petition.

Pfizer's Experimental mRNA Biologic is not a "Vaccine," but is a Gene Therapy

44. These COVID-19 pharmaceutical drugs do not fall under the traditional definition of "vaccine" because they are excluded by their composition.

45. The CDC's definition of vaccine is "a preparation that is used to stimulate the body's immune response against diseases."[19] More specifically, a vaccine is "a suspension of attenuated or killed microorganisms (viruses, bacteria, or rickettsiae), administered for prevention, amelioration, or treatment of infectious diseases."[20]

46. Pfizer-BioNTech's experimental mRNA biologic is among the first of its kind, utilizing a brand-new delivery system and gene therapy technology. Unlike vaccines that have come

[19] *Immunization: The Basics,* Centers for Disease Control and Prevention, available at https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm.
[20] *Vaccine,* The Free Dictionary – Medical Dictionary, available at https://medical-dictionary.thefreedictionary.com/vaccine.

before it, the Pfizer-BioNTech biologic does not contain SARS-CoV-2, the virus that causes COVID-19, but rather consists of mRNA that infiltrates the body's cells and yields the production of a spike protein that mimics the SARS-CoV-2 coronavirus.

47. The FDA has misled government leaders, health care providers, and the public by branding Pfizer-BioNTech's COVID-19 mRNA biologic as a "vaccine." This is an inaccurate statement that has led to false confidence in the safety of the experimental technology.

48. The CDC even went so far as to alter the definitions of "vaccine" and "vaccination" to broaden the scope of what falls under those terms.

49. Prior to the change, a "vaccine" was defined as "a ***product*** that stimulates a person's immune system ***to produce immunity*** to a specific disease, thereby ***protecting*** against that disease." Under the new definition, a vaccine is "a ***preparation*** used to ***stimulate the body's immune response*** against a specific disease".[21]

50. The original definition of "vaccination" was "the act of introducing a vaccine into the body to ***produce immunity*** to a specific disease." Compare that to the new definition, which states that vaccination is "the act of introducing a vaccine into the body to ***produce protection*** from a specific disease."[22]

51. The CDC and FDA have orchestrated a guise under which a product that confers neither

[21] *Why has the CDC changed the definition of a vaccine?,* Verificat, September 29, 2021, available at https://www.verificat.cat/vaccines/entry/why-has-the-cdc-changed-the-definition-of-a-vaccine.

[22] The CDC Suddenly Changes the Definition of "Vaccine" and "Vaccination," Citizens Journal, September 13, 2021, https://www.citizensjournal.us/the-cdc-suddenly-changes-the-definition-of-vaccine-and-vaccination/.

immunity nor protection is considered a "vaccine."

52. However, while not a "vaccine," this biologic does fall under the FDA Office of Cellular, Tissue, and Gene Therapies' definition of "gene therapy products."

53. EUAs are particularly risky in the COVID-19 vaccine context as all three available vaccines are gene therapies.

54. Moderna, in its 2020 filing to the Securities and Exchange Commission, stated: "Currently, mRNA is considered a gene therapy product by the FDA."[23] Pfizer acknowledged the same in its SEC filing.[24]

55. Gene therapies are defined as "[p]products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient."[25]

56. To date, gene therapy vaccines have been used in cancer patients and those with inherited metabolic disorders, whose risk profile is radically different from that of healthy children and adults. ***They have never been used widely in a general population.***

57. FDA's guidance to industry on gene therapy, issued in January 2020 as COVID vaccine

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[23] *Moderna, Inc., United States Securities and Exchange Commission, Form 10-Q,* Quarterly Report Pursuant to Section 13 or 15(D) of the Securities Exchange Act of 1934 (for the quarterly period ended June 30, 2020), *ttps://www.sec.gov/Archives/edgar/data/1682852/000168285220000017/mrna-20200630.htm.*

[24] *BioNTech SE*, United States Securities and Exchange Commission, Form F-1 Registration Statement, filed Sept. 9, 2019, https://www.sec.gov/Archives/edgar/data/1776985/000119312519241112/d635330df1.htm.

[25] *Manufacturing of Gene Therapies: Ensuring Product Safety and Quality,* FDA (2006), available at https://www.fda.gov/media/81682/download.

development was commencing, states:

> "FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing (Ref. 2), and ex vivo genetically modified human cells. **Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. § 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings."**[26]

58. Because this is a novel technology being used on new populations, it is exceptionally important that the FDA apply both its specific gene therapy scientific criteria and general biologic standards in evaluating safety and efficacy.

59. The mechanism of gene therapy vaccines differs substantially from all other vaccines that have ever been used as they work on the premise of gene delivery.

60. Gene therapy COVID vaccines involve a modified virus or an encapsulated segment of RNA entering human cells and utilizing the host cell machinery to produce spike protein. This is an entirely different mechanism than that of traditional vaccines such as inactivated, attenuated, subunit or protein-based vaccines that do not penetrate human cells.

61. The gene therapy standards are more stringent than the criteria FDA applies to vaccines generally. Upon information and belief, the FDA did not apply these standards, including long-term safety follow-up, in the EUA approval process.

62. The failure to examine and regulate COVID-19 vaccines as gene therapy products,

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[26] *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*, U.S. FOOD & DRUG ADMINISTRATION, Guidance Document (Jan. 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemistry-manufacturing-and-control-cmc-information-human-gene-therapy-investigational-new-drug.

particularly for young children, constitutes arbitrary and capricious action and should have prevented the FDA from issuing EUAs initially.

63. Furthermore, the FDA is required to perform an environmental assessment for gene therapy products.[27] Because gene therapy vaccines may shed or spread genetic material into the environment, manufacturers are required to supply data to FDA for review. There is no evidence that such data were provided, nor that the FDA conducted the required environmental assessment as it must according to its own guidelines.

Constitutional Origins, Informed Consent, and Citizen Participation

64. In addition to the Informed Consent principle, the First Amendment guarantees the right to petition one's government and the necessity of robust debate following strict scientific standards. Further, the APA limits what drugs and biologics can be authorized, the purposes they can be authorized for, the individuals they can be prescribed for, and the notices and consent required before they can be administered. The Emergency Use Authorization statute, 21 U.S.C § 360bbb-3, further codifies these standards, including the obligation of Informed Consent derived from the Nuremberg Code.

65. Born of this informed consent, democratically-driven process, the FDA biologic authorization and approval process outlines protocols with public input and robust debate, citizen petition and judicial oversight, substantive limits on its methodology and procedural requirements. Only a rigorous scientific review with meaningful public participation, through citizen petitions answered by the FDA, could even authorize the introduction of a

[27] *Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products: Guidance for Industry,* FDA (March 2015), available at https://www.fda.gov/media/91425/download.

novel biologic. As President Biden advised, no citizen should take a drug without "transparency, transparency, transparency" from the government.[28]

66. The FDA has spectacularly failed to fulfill that promise, and in doing so has also blocked out the public from meaningful participation to ensure that the processes through which the FDA conducts its investigations, which form the foundation for all public health policies regarding COVID-19, are dependable, accurate, and truthful.

67. Exceptional situations should not give an unelected federal agency the authority to abrogate the Constitutional rights of the people.

Vaccine Adverse Events Reporting System: Unprecedented Alarm Signals

68. More than a year after the COVID-19 biologics have been introduced to the American public *en masse*, the reports of adverse events and death from the injections are staggering, and far exceeds that which has been seen from any vaccine in human history.

69. Data released January 14, 2022 by the Centers for Disease Control and Prevention (CDC) showed that since Dec. 14, 2020, a total of 1,214,267 adverse events following injection were reported to the Vaccine Adverse Event Reporting System (VAERS), with 23,978 deaths reported.[29] These numbers far exceeds those of any other vaccine in human history.

70. The Vaccine Adverse Event Reporting System (VAERS) is a 30-year-old voluntary adverse event reporting system for vaccines, jointly managed by FDA and CDC. Injured parties, their healthcare providers and others may file reports. Doctors and vaccine

[28] Biden White House Pledges Data, Transparency, Respect for Free Press, Reuters (January 20, 2021), available at https://www.reuters.com/article/us-usa-biden-briefing-idUSKBN29Q08S.

[29] Vaccine Adverse Event Reporting System (VAERS), CDC Wonder, available at https://wonder.cdc.gov/controller/datarequest/D8;jsessionid=67A4CC1D3E7D207433E5332EABDF.

manufacturers are mandated to report severe injuries and deaths that may be linked to vaccination. This is the nation's foremost adverse event reporting system, despite its inadequacies.

71. According to senior CDC and FDA scientists, "During 2011-2014, VAERS averaged around 30,000 U.S. reports annually, with 7% classified as serious. Healthcare professionals submitted 38% of reports, vaccine manufacturers 30% and patients and parents 14%."[30]

72. CDC and FDA have both said that VAERS is suitable for providing early warnings of vaccine side effects but cannot be used to establish causality. Warning signals must therefore be investigated using other methods, which are believed to be more accurate and complete. According to the article cited above, "VAERS is primarily a safety signal detection and hypothesis generating system. Generally, VAERS data cannot be used to determine if a vaccine caused an adverse event."[31]

73. How the reporting rate of adverse events to VAERS compares with the actual rate of vaccine-associated adverse events is unknown. The same CDC and FDA authors confirmed this, stating, "VAERS lacks information on total number of individuals vaccinated and total number who experience an adverse event, as well as incidence of adverse events in unvaccinated individuals." The authors further emphasized this critical point: "Reporting efficiency, which is the proportion of adverse events that actually get reported to VAERS, is unknown…."

74. Past attempts to investigate the VAERS reporting rate have suggested that between 1%

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[30] *Citizen Petition from Scientific Advisory Board on behalf of Children's Health Defense,* Food and Drug Administration (May 16, 2021), available at https://www.regulations.gov/document/FDA-2021-P-0460-0001.
[31] *Id.*

and 13% of actual adverse effects get reported; however, because CDC changed VAERS reporting recently to include additional data, it is not possible to estimate the degree of underreporting based on past attempts to do so. [32]

75. The CDC has failed to account for this underreporting in its representation of VAERS data, underestimating the number of adverse events to the public and thus ignoring the actual prevalence of COVID-19 biologic harm.

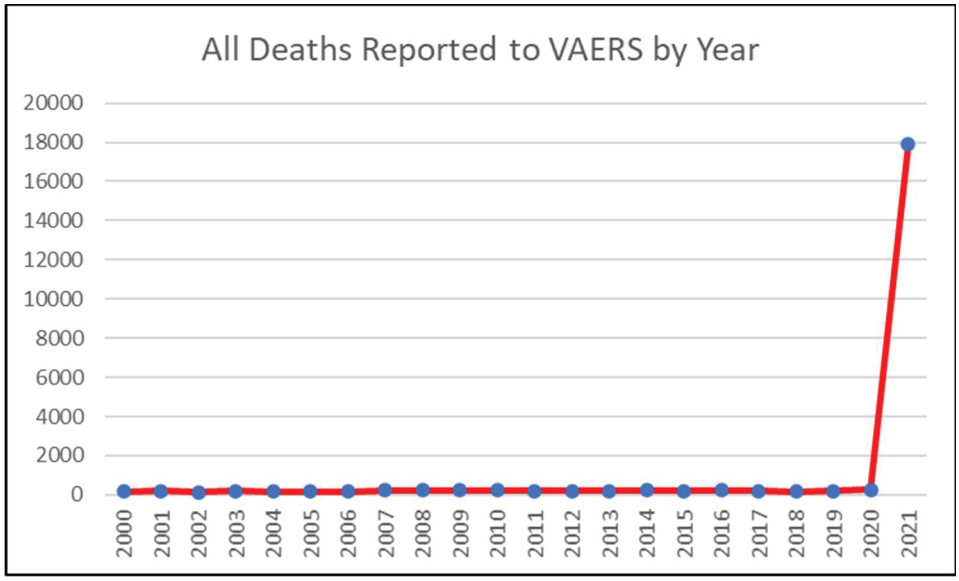
76. Even when strong scientific evidence has been presented of their misconduct, CDC and FDA have refused to issue any corrections, and continue to misrepresent the VAERS data as if VAERS reporting rates reflected accurate adverse event rates.

77. The VAERS data on myocarditis and pericarditis are especially concerning, with 11,132 and 7,233 cases reported respectively as of January 14, 2022.[33] The absence of data from other FDA- and CDC-accessible databases ought to be alarming. With over 60% of the United States vaccinated, it is inexplicable that we still do not know the actual rates of myocarditis in the population. This information may be being concealed to garner licenses for the vaccines in the pediatric population.

78. Furthermore, the input of event reports to VAERS since the COVID vaccines were rolled out is ***greater than all cumulative adverse event reports to VAERS for the prior thirty years***: an alarming statistic. Death reports for 2021 are also greater than cumulative deaths reported to VAERS over the preceding 30 years. To the FDA, this is a taboo subject since

[32] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J. 2004 Apr;23(4):287-94. doi: 10.1097/00006454-200404000-00002. PMID: 15071280.
[33] Vaccine Adverse Event Reporting System (VAERS), CDC Wonder, available at https://wonder.cdc.gov/controller/datarequest/D8;jsessionid=67A4CC1D3E7D207433E5332EABDF.

no public health official has explained this. The CDC, which is charged with investigating every reported death in VAERS, simply waves its hands and claims none are due to vaccination, without providing any data.



79. Although VAERS cannot be used to accurately calculate the rates of any adverse reaction due to the underreporting inadequacy, CDC did exactly that for anaphylaxis, claiming the rate of VAERS reporting was the rate of occurrence, even though it was almost guaranteed to be an underestimate.[34]

80. When a high-quality study of Massachusetts General Hospital and Brigham hospital employees showed that anaphylaxis occurred in 250 per million employees,[35] CDC failed to update its website and still claims, as of October 18, 2021, that anaphylaxis occurs only 2-5

[34] Meryl Nass, *Did CDC Deliberately Mislead Public on Allergic Reactions to Moderna Vaccine?,* The Defender (January 28, 2021) available at https://childrenshealthdefense.org/defender/did-cdc-mislead-public-allergic-reactions-moderna-vaccine/.

[35] Blumenthal KG, Robinson LB, Camargo CA, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. *JAMA.* 2021;325(15):1562–1565. doi:10.1001/jama.2021.3976.

times per million COVID vaccines.[36] Which begs the question: how accurate are CDC's other adverse event rates?

81. CDC has made a number of changes to its standard practices since the beginning of the pandemic. Here is just one example: beginning on May 1, 2021, for CDC to accept a report of a "breakthrough" case, or a case of COVID in a vaccinated individual, the infected person must have required hospitalization or died *and* had their infection confirmed with a PCR test using 28 or fewer cycles.[37] Other problems with data acquisition of breakthrough cases[38] have further contributed to keeping the official number of such cases much lower than they really are. In the UK, in all age cohorts of 30 years and up, there is a higher rate of COVID cases in the vaccinated compared to the unvaccinated.[39]

[36] *Selected Adverse Events Reported after COVID-19 Vaccination,* Centers for Disease Control and Prevention (Nov. 30, 2021) available at https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
[37] *Ensuring COVID-19 Vaccines Work,* Centers for Disease Control and Prevention (Novhttps://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html
[38] Erin Banco, *Holes in reporting of breakthrough Covid cases hamper CDC response,* Politico (August 25, 2021) available at https://www.politico.com/news/2021/08/25/cdc-pandemic-limited-data-breakthroughs-506823.
[39] COVID-19 Vaccine Surveillance Report – Week 42, UK Health Security Agency, availabe at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1027511/Vaccine-surveillance-report-week-42.pdf.

COVID-19 vaccine surveillance report – week 42

Table 2. COVID-19 cases by vaccination status between week 38 and week 41 2021

Cases reported by specimen date between week 38 and week 41 2021	Total	Unlinked*	Not vaccinated	Received one dose (1-20 days before specimen date)	Received one dose, ≥21 days before specimen date	Second dose ≥14 days before specimen date	Rates among persons vaccinated with 2 doses (per 100,000)	Rates among persons not vaccinated (per 100,000)
Under 18	397,882	24,292	351,148	10,698	11,001	743	314.1	3,013.6
18-29	62,885	7,512	20,902	758	8,404	25,309	462.1	615.4
30-39	92,257	7,346	21,726	636	6,545	56,004	956.7	751.1
40-49	130,904	7,297	13,022	293	3,800	106,492	1,731.3	772.9
50-59	88,020	4,790	5,399	80	1,632	76,119	1,075.3	528.6
60-69	45,155	2,614	1,872	24	617	40,028	704.1	347.1
70-79	27,360	1,559	658	12	215	24,916	537.9	267.6
≥80	11,907	854	382	7	215	10,449	406.8	304.1

* Individuals whose NHS numbers were unavailable to link to the NIMS

** Interpretation of the case rates in vaccinated and unvaccinated population is particularly susceptible to changes in denominators and should be interpreted with extra caution

82. One 12-year-old, Maddie de Garay, was healthy when she volunteered to enter Pfizer's pediatric COVID vaccine trial at the University of Cincinnati with her two siblings, believing that she was helping her country solve the COVID crisis. She became ill immediately after the second dose with high fever and then a wide range of symptoms. Over the subsequent six months, she had about a dozen ER visits and six hospitalizations. She has required a feeding tube to be nourished and uses a wheelchair. Dr. Frenck, the Principal Investigator for the Pfizer pediatric clinical trial at his hospital, was her physician and is aware of these problems. Yet Maddie de Garay was not reported as a serious adverse event in the trial documents, and when her trial data were published in the New England Journal of Medicine, there were no serious vaccine-related adverse events listed for any subject. Dr. Frenck, Maddie's physician, was the first author of the NEJM study. How many other subjects in Pfizer's trials were similarly injured, but went unreported? How many Principal Investigators issued positive reports despite knowing of severe injuries?

83. According to VAERS, FDA actions have buried people in addition to data. The FDA has

not shared actual data on efficacy, side effects and all injuries to educate the public on the risks of these vaccines. Nor have they seemingly utilized this information effectively via risk assessments and safety analyses when granting EUAs.

Far-Reaching and Long-Lasting Potential Side Effects

84. There is a myriad of short-term vaccine side effects that have been witnessed and reported since the rollout of the vaccine. However, scientists and health care professionals have long been raising the alarm over the long-term implications that this mRNA gene therapy technology can have on a recipient's health.

85. In truth, we know nothing about the long-term risk of the COVID-19 biologic in children. This biologic tested on human subjects for less than five months of data collection in Phase II and III clinical trials before being administered to the public under an EUA.[40]

86. COVID-19 vaccines have not gone through testing for genotoxicity, mutagenicity, teratogenicity, and oncogenicity by the FDA's own admission.[41] In plain English, no one can be assured that these products don't cause birth defects, infertility, or cancer; the so-called experts just don't know. This alone should deprive these products of licensure and EUA status given these severe potential risks, especially for children who should have the greatest number of years ahead of them.

87. We now know that vaccine-induced spike proteins, the putative antigen induced by Pfizer-BioNTech COVID vaccine, are a toxin. They are produced and enter the circulatory system, have predictable negative consequences to vascular endothelium, they activate

[40] *About Our Landmark Trial,* Pfizer, available at https://www.pfizer.com/science/coronavirus/vaccine/about-our-landmark-trial.
[41] Package Insert – Comirnaty, FDA (8/2021), available at https://www.fda.gov/media/151707/download.

platelets, and cross the blood-brain barrier. Spike proteins circulate throughout the body and accumulate in large concentrations in organs and tissues, including the spleen, bone marrow, liver, adrenal glands, and especially the ovaries.[42] Since there exists no way to turn off spike production, the actual dose of spike protein may vary by orders of magnitude from person to person, which raises concern regarding the FDA's methods of determining dosage.

88. The potency of the product cannot be established nor the duration of time during which it is effective. This is a regulatory conundrum that the FDA has not solved. Since measuring potency is required for all drugs and biologics, it must solve this problem before any licensure, thus requiring vacatur of the EUA for the Pfizer-BioNTech COVID-19 vaccine for this age group.

89. In addition, spike proteins would be expected to trigger the destruction of cells that produce it and present it on their surfaces. Products that induce the production of spike protein should only be used after careful consideration of the individual recipient's risks and benefits. They should not be employed in mass vaccination programs where there is no learned practitioner to weigh appropriate use, nor in individuals with a very low risk of serious COVID disease.

90. Furthermore, strong but not yet conclusive evidence links spike protein *in vivo* to blood clots, thrombocytopenia, hemorrhages, heart attacks and strokes, the very severe effects of COVID-19 disease itself. The damage the spike protein may be causing must be fully elucidated. The toxicity of the spike protein means that no vaccine using this design can be assumed to be safe until proven otherwise, and none should continue under an EUA or be

[42] *SARS-CoV-2 mRNA Vaccine Biodistribution Study*, https://www.docdroid.net/xq0Z8B0/pfizer-report-japanese-government-pdf.

licensed.

91. Studies have also shown that antibody-dependent enhancement ("ADE") poses a severe threat to vaccinated individuals.[43] "ADE occurs when the antibodies generated during an immune response recognize and bind to a pathogen, but they are unable to provide infection. Instead, these antibodies act as a 'Trojan horse,' allowing the pathogen to get into cells and exacerbate the immune response."[44] Thus, when dealing with different strains of COVID-19, ADE caused by the COVID-19 biologic may accelerate the virus infecting the cells and resulting in more severe illness. Therefore, children who receive the COVID-19 biologic are at risk of *increased severity* if they are exposed to similar viruses.

92. In addition, the myocarditis risk immediately after vaccination in older children is considerable, potentially life-threatening, and increases exponentially with decreasing age, suggesting that young children are at particularly high risk.

93. The pediatric clinical trials are too small to quantify the risk from myocarditis and most other adverse events. Indeed, in the approval for Pfizer's Comirnaty vaccine, the FDA ordered further studies into myocarditis and pericarditis (Exh. 6).[45] As FDA acknowledged when discussing its post-marketing requirements for its Comirnaty vaccine, "[w]e have determined that an analysis of spontaneous post-marketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious

[43] Infection-enhancing anti-SARS-CoV-2 antibodies recognize both the original Wuhan/D614G strain and Delta variants. A potential risk for mass vaccination? Yahi, Nouara et al.Journal of Infection, Volume 83, Issue 5, 607 - 635, doi: https://doi.org/10.1016/j.jinf.2021.08.010.
[44] *Antibody-dependent Enhancement and Vaccines,* Children's Hospital of Philadelphia, available at https://www.chop.edu/centers-programs/vaccine-education-center/vaccine-safety/antibody-dependent-enhancement-and-vaccines.
[45] *BLA Approval,* U.S. Food and Drug Administration (August 23, 2021), available at https://www.fda.gov/media/151710/download.

risk of subclinical myocarditis. Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks."[46]

94. FDA told BioNTech-Pfizer that since FDA was unable to assess the myocarditis risk, it expected BioNTech-Pfizer to do so. FDA wants Pfizer's final reports on myocarditis to be submitted in 2024 and 2025. It is unacceptable to ponder the inevitability that tens or hundreds of millions of the world's children will be vaccinated before BioNTech-Pfizer tells us to what extent their vaccines damage children's hearts, if this EUA is allowed to continue.

95. According to the Jerusalem Post on October 7, 2021, the health ministry was considering whether "individuals vaccinated with the Pfizer coronavirus vaccine may be asked to avoid strenuous exercise [including swimming] and other physical activity for one week after receiving each dose due to cases of myocarditis…."[47]

96. Four Nordic countries recently halted the use of Moderna's vaccine in some age groups due to the risk of myocarditis. It was reported by the Wall Street Journal that FDA paused its review of the Moderna vaccine for teenagers in response to the Nordic countries' action. The article was subtitled, "Agency holds off decision on expanding use of shot to 12-to-17-year-olds while it looks into risk of rare heart condition."[48]

97. FDA should have held off its expansion of the Pfizer shot to 5-to-11-year-olds until it

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[46] *BLA Approval,* U.S. Food and Drug Administration (August 23, 2021), available at https://www.fda.gov/media/151710/download.

[47] Maayan Jaffe-Hoffman, *Health Ministry to consider asking newly vaccinated to avoid working out,* The Jerusalem Post (October 7, 2021), available at https://www.jpost.com/health-and-wellness/health-ministry-to-consider-asking-newly-vaccinated-to-avoid-working-out-681317/.

[48] *FDA Delays Moderna Covid-19 VAccine for Adolescents to Review Rare Myocarditis Side Effect,* The Wall Street Journal (October 15, 2021), https://www.wsj.com/articles/fda-delays-moderna-covid-19-vaccine-for-adolescents-to-review-rare-myocarditis-side-effect-11634315159.

has completed this review since Pfizer's shot also causes myocarditis.

98. The bottom line is that we have no idea of either the short or long-term risk of the Pfizer vaccine in 5-to-11-year-old children, but it is reasonable to assume the risk of myocarditis could be considerable. Other risks have not been quantified but could also be substantial. We do not even know their magnitude in adults, after 6.8 billion COVID vaccinations have been administered throughout the world.[49] It cannot be justified to vaccinate children with a biologic for which the world's public health professionals have failed to collect and analyze the most rudimentary data on safety during the largest rollout of (mostly experimental) pharmaceutical products in the history of the world.

99. While there is no justification for pediatric vaccinations, as herd immunity is impossible to achieve with current vaccines, there is a substantially high and concerning risk of several adverse effects, including death. The FDA is therefore encouraging superfluous vaccination that will put children at more risk of vaccine harm than they face from COVID-19.

Vaccination of Children is not Medically Necessary

100. The real-world experience of gene therapy vaccines continues to undermine claims of efficacy. The efficacy of the Pfizer vaccines is now estimated to be under 50%, even though public health officials set 50% as the minimum efficacy level required.[50]

101. The Biden Administration has already called for "booster" shots because of this waning effectiveness. These children are being set up for a lifetime of booster shots for subverted immune systems.

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[49] *More than 8.22 Billion Shots Given:Covid-19 Tracker,* Bloomberg (December 6, 2021), available at https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/.
[50] Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry, available at *https://www.fda.gov/media/139638/download.*

102. The Court must take action to protect children from what may be crimes against humanity. Waiting around for the law enforcement arm of FDA, the Office of Criminal Investigations, to conduct a criminal investigation against itself is futile.

103. The risks demonstrably outweigh the benefits of COVID vaccination for young children. The actual risk of hospitalization, death, and multisystem inflammatory syndrome (MIS-C) from COVID-19 in children aged 5-11 years is the lowest for severe disease and death than all other age cohorts. The risk of death and severe illness in children or young adults is exceptionally rare.[51] Children are usually asymptomatic or mildly symptomatic from COVID infections. As such, Pfizer cannot make accurate conclusions about the impact on hospitalizations or severe illness in children 5 to 11 years old.

104. John Hopkins faculty member Marty Makary published an Op-Ed in the Wall Street Journal detailing the finds when he and a research team reviewed about 48,000 cases of children under 18 reported to have COVID-19 between April and August of 2020.[52] Their findings were shocking: a mortality rate of zero among children without a pre-existing medical condition.[53]

105. According to the Associated Press, the FDA required what is called an immune "bridging" study — evidence that the younger children developed antibody levels already proven to be protective in teens and adults — and that's what Pfizer reported in a press

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[51] Clare Smith, David Odd, *Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: a national study using linked mandatory child death reporting data,* (July 7, 2021), doi: https://doi.org/10.21203/rs.3.rs-689684/v1.
[52] *The Flimsy Evidence Behind the CDC's Push to Vaccinate Children,* The Wall Street Journal (July 19, 2021), available at https://www.wsj.com/articles/cdc-covid-19-coronavirus-vaccine-side-effects-hospitalization-kids-11626706868.
[53] *Id.*

release, not a scientific publication.[54]

106. By comparison, scientific authors found the bulk of normalized post-vaccination deaths occurred mostly in the elderly with high comorbidities, while the normalized post-vaccination deaths were small, but not negligible, in children. Dr. Peter Marks, FDA chief, said the pediatric studies should be large enough to rule out any higher risk to young children.[55] Yet, Pfizer's study isn't large enough to detect any extremely rare side effects, such as the heart inflammation that sometimes occurs after the second dose, mostly in young men, Marks said.[56]

107. CDC tries to counter that there is a real danger to children from COVID-19. Exaggerated reports such as CDC reports 94 COVID-19 deaths *with COVID* since January 1, 2020 in the 5 through 11 age group are inaccurate since CDC designates these as deaths "involving COVID" or "with COVID" rather than *due* to COVID.[57]

108. The October 2021 *Pediatrics* issue included a report by David McCormick et al. showing that of 112 pediatric deaths associated with SARS-CoV-2, 86% had comorbidities, especially obesity, neurologic and developmental conditions. The mean age of decedents was 17.[58]

109. It is impossible to separate deaths *with* COVID from those *due* to COVID in the U.S.

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[54] *Pfizer says COVID-19 vaccine works in kids ages 5 to 11,* AP News, available at https://apnews.com/article/business-science-health-coronavirus-pandemic-coronavirus-vaccine-202cb6e44b90270ec4d1f19690ed94c5.
[55] *Ibid.*
[56] *Ibid.*
[57] *Weekly Updates by Select Demographic and Geographic Characteristics,* CDC National Center for Health Statistics, https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm.
[58] David W. McCormick, LaTonia Clay Richardson, Paul R. Young, et al., Deaths in Children and Adolescents Associated With COVID-19 and MIS-C in the United States. *Pediatrics* November 2021; 148 (5): e2021052273. 10.1542/peds.2021-052273

because the CDC does not distinguish them. But what we do know is that child deaths due to COVID in Germany, according to the BILD newspaper, were a total of 20 by May 2021, in a country with 85 million people. Pediatric deaths were "under 30" through March 2021 according to the UK government, with 60 million people.[59]

110. Regarding MIS-C, the data are sparse. The U.K.'s Joint Committee on Vaccination and Immunisation (JCVI) stated on September 3, 2021, based on data from the UK, Canada and the US[60]:

> "There are no clinical trial data of vaccine efficacy against PIMS-TS [MIS-C], nor any real-world estimates of vaccine effectiveness. Post-COVID-19 syndrome (often called 'long COVID') has been reported in children and young people. Existing studies suggest that longer term (≥8 weeks) symptoms following SARS-CoV2 infection occur in about <1% to 10% of persons after COVID-19, with controlled studies generally reporting rates at the lower end of this range."

111. In one report in *Hospital Pediatrics*,[61] of 146 hospitalized pediatric COVID cases during 5 months in 2020, only 20 (14%) were deemed "significantly symptomatic." Only 24 actually *admitted* because of COVID. Of those significantly symptomatic, 60% were obese and 35% had asthma. COVID-19 was either incidental or minimally related to the reason for hospitalization in 86% of the admissions. Of the 4 pediatric deaths in this series, only one was attributed to COVID by the authors, in a "medically complex patient admitted for respiratory failure."

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[59] *JCVI Statement on COVID-19 Vaccination of Children and young People Aged 12 to 17 years,* UK Department of Health and Social Care (August 4, 2021), available at https://www.gov.uk/government/publications/jcvi-statement-august-2021-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years/jcvi-statement-on-covid-19-vaccination-of-children-and-young-people-aged-12-to-17-years-4-august-2021.

[60] *Ibid.*

[61] Webb NE, Osburn TS. Characteristics of Hospitalized Children Positive for SARS-CoV-2: Experience of a Large Center. Hosp Pediatr. 2021 Aug;11(8):e133-e141. doi: 10.1542/hpeds.2021-005919. Epub 2021 May 19. PMID: 34011567.

112. Pediatric vaccinations cannot be justified as necessary for herd immunity when herd immunity itself is impossible to achieve with current vaccines. Given the rapid waning of protection and the inability of current vaccines to prevent transmission of SARS-CoV-2, admitted by CDC Director Walensky,[62] it is not possible to achieve herd immunity with vaccination. In fact, the U.K.'s head of the Oxford Vaccine Group, Professor Sir Andrew Pollard, told Parliament that herd immunity due to vaccination was a myth, and "not a possibility."[63]

113. While protecting the elderly has sometimes been used as the justification for vaccinating children (for example, against influenza) it is unethical to have one group take on risk to protect another group. It is even more problematic when the group being asked to assume the risk, children, cannot give informed consent on their own behalf. When the magnitude of the risk is significant (of myocarditis, for example) but has not been quantified, and the long-term risks of vaccination are unknown, demanding that children shoulder this risk for others is ethically untenable.

114. Furthermore, natural immunity is broader and longer lasting than immunity derived from current COVID vaccines.[64] From exposure to COVID-19 over the past 2 years, natural immunity occurs in 40% of children, a higher proportion than in any other age group. They

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[62] Kyle Becker, *CDC Director Changes Her Story, Now Admits COVID Vaccines Don't Prevent Virus Transmission,* Becker News (August 6, 2021), available at https://beckernews.com/walensky-180-40752/.

[63] Mychael Schnell, *Herd Immunity 'Not a Possibility' with Delta Variant, Oxford Vaccine Group Head Says,* The Hill (August 11, 2021), available at https://thehill.com/policy/healthcare/567414-herd-immunity-not-a-possibility-with-delta-variant-oxford-vaccine-group.

[64] Kristen Cohen, Susanne Linderman, Zoe Moodie, et al., *Longitudinal analysis shows durable and broad immunity memory after SARS -CoV-2 infection with persisting antibody responses and memory B and T cells,* Cell Reports Medicine, July 14, 2021, DOI: https://doi.org/10.1016/j.xcrm.2021.100354.

were tested using anti-nucleocapsid antibodies. Since then, they have had a summer in which to play together and two months of in-person schooling, and their immunity could be approaching 50%. Vaccinating these children will expose them to excess risk without the prospect of benefit, as vaccination when one has natural immunity is contraindicated. This is sheer nonsense.

115. FDA allows Pfizer to use anti-nucleocapsid antibody tests to identify and exclude prospective subjects for clinical trials who have preexisting immunity; they cannot be included in the efficacy analysis. Yet Americans are forbidden from demonstrating they are immune, since the FDA and CDC do not allow ordinary American children or adults to use the identical test to demonstrate that they are already immune and don't need vaccination for COVID-19. An infinitesimally small percentage of children require COVID vaccination.

116. Given that nearly half of all children have natural immunity to COVID, according to the CDC, there is no ethical justification for superfluous vaccination that will put children at elevated risk of vaccine harm.[65]

The FDA is Facilitating the Big Pharma Monopoly

117. Pfizer is projected to earn $36 billion dollars this year in vaccine sales, and more than that next year; indeed, Pfizer expects to make almost as much from COVID-19 vaccines alone as it did for all products in 2020.[66] To say that there is a conflict of interest here is an

[65] *Vaccines and Related Biological Products Advisory Committee October 26, 2021 Meeting Announcement,* FDA (October 26, 2021), available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-26-2021-meeting-announcement.

[66] Jake Epstein, *Pfizer Expects to Make Nearly as Much Revenue Just From COVID-19 Vaccines in 2021 as it Earned in All of 2020,* Business Insider (Nov. 2, 2021), available at

understatement. It is naive to think Pfizer-BioNTech will try to identify the actual rate of myocarditis in children when so much money is at stake. Pfizer is the world's largest drug company. It is also noteworthy that Pfizer has paid more in fines to federal and state governments than any other pharmaceutical company. In 2009, Pfizer was ordered to pay a criminal fine of $1.195 billion as part of one of the biggest fraud settlements in the US for misbranding a pharmaceutical product with the intent to defraud or mislead; this is the largest criminal fine ordered in the United States *ever.*[67] This evidence suggests that Pfizer is neither reliable nor trustworthy.

118. Pfizer contracted with the US government, which has possession of all COVID vaccines across the country. An October 19, 2021, Public Citizen report titled Pfizer's Power, discussing Pfizer and its COVID vaccine contracts notes:

> ". . . neither Pfizer nor the U.S. government can make 'any public announcement concerning the existence, subject matter or terms of this Agreement, the transactions contemplated by it, or the relationship between the Pfizer and the Government hereunder, without the prior written consent of the other.' The contract contains some exceptions for disclosures required by law."

119. Furthermore, one of the FDA's briefers who failed to find adverse event signals in the Vaccine Safety Datalink (VSD) was Nicola Klein, who is the Principal Investigator (PI) in multiple COVID vaccine studies for Pfizer conducted in both adults and children. Those Pfizer clinical trials have brought in many millions of dollars to her institution. This conflict

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https://www.businessinsider.com/pfizer-2021-vaccine-revenue-close-to-2020-total-earnings-2021-11.

[67] *Justice Department Announces Largest Health Care Fraud Settlement in its History,* US Department of Justice (September 2, 2009), available at https://www.justice.gov/opa/pr/justice-department-announces-largest-health-care-fraud-settlement-its-history.

of interest was undisclosed.[68]

120. What we don't know yet, or haven't been told, is critically important. In furtherance of a clandestine deal, FDA rushes the shots into young children.

121. Unethical coercive pressure will be applied to children and their parents, as has occurred with older children and adults, to receive these EUA vaccines. To grant authorization is to abet unethical coercion that violates the Nuremberg Code's first principle that informed consent of the individual is "absolutely essential," without duress or coercion.

122. There is no available care for children injured by COVID shots. The science and medicine have not yet developed, and most families will be unable to cover the costs of potential catastrophic injuries.

123. Obviously, the deck is stacked. Policies were put in place such that we will never know the risks of COVID vaccinations nor be apprised of the magnitude of those risks.

124. Some children likely will die or be permanently injured from these vaccines based on the authorization for children 5-to-11-year-olds.

125. In an act of true salesmanship, the FDA exaggerated the harms to children from COVID-19 and magnified the benefits of vaccination to claim that benefit exceeds risk. This was accomplished via datasets that inexplicably failed to yield adverse event signals, conflating deaths and hospitalizations "with" COVID as if all were "due to" COVID, ignoring the existence of naturally acquired immunity and making overly optimistic assumptions about the efficacy and duration of vaccine-induced protection. However, if you use more realistic data, such as presented here, the risk exceeds benefit in the 12-15 age group and will exceed

[68] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. *JAMA.* 2021;326(14):1390–1399. doi:10.1001/jama.2021.15072.

benefit in the 5-to-11-year age group also.

Attack on the Unvaccinated

126. FDA's authorization of the Pfizer COVID-19 vaccine for children is leading to egregious discrimination against unvaccinated children that has the potential to pose far more of a health risk to children than COVID-19.

127. Children in Texas are being denied medical services, including transplants, without vaccination. This is purely due to FDA's authorization and its misleading and false claim that the product available to children is fully licensed and FDA approved for adults.

128. This erroneous narrative has led hospitals, medical clinics, and schools to implement COVID-19 vaccination policies for young children.

129. Defendants once again granted this authorization for an experimental injection knowing full well that their actions are destined to result in nationwide-school vaccine mandates and inclusion on childhood vaccine schedules. States have already set the precedent for compulsory immunizations to attend public and private schools from kindergarten up through secondary education; a COVID-19 vaccine mandate for children following authorization is inevitable in some locations. For example, California's Governor Gavin Newsom has already made it clear that students in kindergarten through sixth grade would be phased into the state's vaccine mandate requirement, with all students K-12 being required to receive the COVID-19 biologic for the 2022-2023 school year. Other districts in California have begun implementing independent mandates that are stricter than the anticipated state-wide mandate.[69] The harm that may befall a significant number of children

[69] *As LA Schools Backtrack on COVID Vaccine, Dozens More Districts Push to Mandate It*, ABC10 (January 19, 2022), available at https://www.abc10.com/article/news/local/california/as-

in the state of California will occur as a direct result of Defendant FDA's action.

130. Unless and until all children inject these experimental biologics into their developing bodies – often against the children's wishes and without informed consent – they will slowly be pushed out of society, denied an education, and worse. The precedent has already been set for adults, many of whom already have been denied their livelihoods due to their refusal to take a COVID-19 vaccine. All of this is unprecedented, unwise, unnecessary, and unlawful.

131. In what sane society must a child take an experimental drug that fails to protect them from a virus that has an infinitesimal chance of hospitalizing or killing them, to have access to the same services and opportunities as the rest of the population?

132. The risk posed to a child from COVID-19 is not even comparable to the risk posed from not receiving a life-saving transplant or medical service, or even the denial of education or the cultural experience of living life without being asked to show one's papers. The question remains how many children will need to suffer such abuse and discrimination before the FDA will be held accountable for the consequences of their actions.

The Inglorious History of Medical Experiments Continues

133. Born amidst malaria and smallpox pandemics, the Constitution authorized no emergency exception to the liberties secured under it. The Founding Fathers understood the virus of concentrated power posed more of a threat than any biological virus could. The Ninth Amendment to the Constitution safeguarded all ancient rights and liberties, including the ancient tort of battery. *United States Constitution, Amendment IX*. The right against battery

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la-schools-backtrack-on-covid-vaccine-dozens-more-districts-push-to-mandate-it/103-729bbb6b-1a49-4dbd-8909-9f5573aaa73d.

assured "the right of every individual to the possession and control of his own person, free from all restraint or interference of others," which would be "sacred" and protected under the law. *Union Pacific R. Co. Botsford*, 141 U.S. 250, 251 (1891). The famed Justice Benjamin N. Cardozo defined the doctrine as the universal right of every person "to determine what shall be done with his own body." *Schloendorff v. Society of New York Hospital*, 105 N.E. 92, 93 (1914). This right to informed consent incorporates necessarily the right to refuse treatment: "The forcible injection of medication into a nonconsenting person's body represents a substantial interference with that person's liberty." *Washington v. Harper*, 494 U.S. 210, 229 (1990). The Nuremberg Code enshrines the right of informed consent as a matter of universal law, so widely recognized, courts consider it a *jus cogens* legal principle enforceable everywhere. *Abdullah v. Pfizer, Inc.*, 562 F.3d 163 (2d Cir. 2009). Based on these precepts, courts require clear and convincing evidence that a person poses an imminent, severe risk to others before those individuals may be subject to forced medical care. *O'Conner v. Donaldson*, 422 U.S. 563 (1975); *Addington v. Texas*, 441 U.S. 418 (1978).

Eugenics Era

134. We only deviated from this Informed Consent standard of medical care during the Eugenics Era, a diseased doctrine birthed in the medical academies of the United States at the turn of the last century, as a deformed outgrowth of the then in-vogue school of Social Darwinism. A trio of decisions carved out emergency exceptions to Constitutional liberties, including authorizing a fine for not taking a vaccine (*Jacobson v. Massachusetts*, 197 U.S. 11 (1905)), forced sterilizations of poor and politically unprotected populations (*Buck v.*

Bell, 274 U.S. 200 (1927), which relied exclusively on expanding *Jacobson*), and the decisions culminated in the kind of "emergency exception" logic that led a court to authorize forced detention camps based on race alone. *Korematsu v. United States*, 323 U.S. 214 (1944). This trilogy of infamy sees its corpses rise again as "precedents" seemingly permitting governments to reinstate Eugenics-Era logic across the legal landscape.

Nuremberg Code Era

135. Reeling from the moral horror of the Nazi regime, and its enthusiastic embrace of eugenics, American jurists led the way in reestablishing the Constitutional order by invalidating the eugenics-era precedents and by instituting the Nuremberg Code of 1947, whose governing principles of Informed Consent for all matters of medicine form a *jus cogens* principle of universal, internationally recognized law, enforceable amongst all civilized nations. The right to bodily autonomy formed the foundation for Supreme Court recognition of the right to privacy and guided the standards governing all matters of medical care concerning the state. Only clear and convincing evidence of an imminent danger to others justifies forced medical care. *Washington v. Harper*, 494 U.S. 210, 229 (1990); *Addington v. Texas*, 441 U.S. 418 (1978). Only business necessity warrants a place of public accommodation or employer to discriminate against someone based on her perceived medical status. 42 U.S.C. § 12101. The Nuremberg Code-derived governance of medical authority reversed the eugenics-era precedents, empowered individuals with a meaningful participatory role, and empowered democratic oversight, judicial supervision, and procedural safeguards on the medical regulatory process, enshrining informed consent as the ethical foundation of modern medicine and a fundamental human liberty so universal that

courts acknowledge it as a peremptory norm.

Rushed Drugs & Medical Experiments

136. The concern over uninformed, nonconsensual, and pharmacological failures haunts the history of rushed drugs, biologics and negligent courts. From Tuskegee to the military, from the foster homes of young women to Indian health care services on reservations, from facilities for the mentally ill to jails for women, the least powerful and most trusting have been victimized by government medical experimentation, without recourse or remedy. Deceptive denial of syphilis treatment, forced sterilizations, testing of radioactive ingredients on unwitting patients, psychological experimentation on unsuspecting students (such as the MK-Ultra type testing on Ted Kaczynski at Harvard), the LSD testing on government employees, the chemical testing over San Francisco or in New York City subways, the mustard gas secret tests on drafted soldiers – history has taught us that government must be reined in lest it treat its citizenry as rats in a cage or guinea pigs for experimentation.

137. In 1955, regulators rushed approval of a polio vaccine that caused an outbreak of polio in hundreds of children, known as the Cutter Incident. Later scholars attributed the blame to the federal government's failures in rushing the product to market. In 1959, the Belgian Congo rushed another polio vaccine. Twenty-five years later, a new virus emerged in the population: AIDS. Detailed journalistic investigations have attributed it to the use of contaminated monkey kidneys in the development of polio vaccines.[70] In 1963, Americans discovered that the polio vaccine from monkey kidneys contained the Simian Virus 40 that

[70] Edward Hooper, The River: A Journey to the Source of HIV and AIDS (1999).

could cause cancer in humans.[71] In 1976, the Ford administration rushed a vaccine for swine flu. The virus proved less deadly than anticipated, but the vaccine proved far more dangerous, causing thousands of Americans to develop a serious neurological disorder known as Guillain-Barre Syndrome, causing paralysis. As the "60 Minutes" report from the time identified, the FDA was again the source of failure because of the rushed, pressured political environment of the time.[72] Most recently, in 2018, the World Health Organization rushed approval of a vaccine against Dengue Fever, despite warnings from dissident doctors, which left hundreds of children dead and thousands more injured.[73]

Effectiveness of Alternative Treatments

138. Early treatment against COVID is highly effective, but for the FDA to acknowledge this would prevent EUAs from being issued for COVID vaccines and on-patent drugs such as Regeneron's monoclonal antibodies, Gilead's Remdesivir and Merck's Molnupiravir.

139. There are well-studied, safe, approved and readily available medical products to prevent and treat COVID-19. Given all the known and unknown risks of existing COVID vaccines, these alternatives are preferable to vaccination, yet the FDA has failed to rigorously evaluate them let alone encourage their use.

140. These alternatives include Ivermectin, Methylprednisolone, Fluvoxamine, Hydroxychloroquine, Vitamin C, Vitamin D3, Zinc, Aspirin, corticosteroids and other

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[71] Debbie Bookchin and Jim Schumacher, *The Virus and the Vaccine* (July 1, 2005).
[72] 60 Minutes: Swine Flu (1976), available at https://www.youtube.com/watch?v=4bOHYZhL0WQ.
[73] Michaeleen Doucleff, *Rush to Produce, Sell Vaccine Put Kids In Philippines At Risk,* NPR (May 3, 2019), available at https://www.npr.org/sections/goatsandsoda/2019/05/03/719037789/botched-vaccine-launch-has-deadly-repercussions

accessible therapies. Randomized-controlled trials and observations by front line medical experts have confirmed that COVID-19 is preventable and treatable, especially at early onset stages, with medicines and practices that have a decades long utilization proving their safety.[74]

141. Various treatment methods using combinations of such medications have proven effective. There has been substantial and significant progress on early, ambulatory multi-drug therapy for high-risk COVID-19 patients, resulting in as much as 85% reductions in both hospitalizations and death.[75]

142. For example, both Ivermectin and Hydroxychloroquine can be taken in a weekly dose to prevent infection from SARS-CoV-2, with great effectiveness.[76]

143. Ivermectin, whose safety has been established with at least a billion doses administered and which is listed on the WHO's list of essential drugs, along with the chloroquine drugs, has been shown to have substantial prophylactic and treatment capabilities.[77]

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[74] McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection. *Am J Med*. 2021;134(1):16-22. doi:10.1016/j.amjmed.2020.07.003; McCullough PA, Alexander PE, Armstrong R, et al., Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev Cardiovasc Med. 2020 Dec 30;21(4):517-530. doi: 10.31083/j.rcm.2020.04.264. PMID: 33387997.

[75] McCullough PA, Alexander PE, Armstrong R, et al., Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Rev Cardiovasc Med (2020) 21:517–530. doi10.31083/j.rcm.2020.04.264.

[76] McCullough PA, Kelly RJ, Ruocco G, et al., *Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection*. Am J Med. 2021 Jan;134(1):16-22. doi: 10.1016/j.amjmed.2020.07.003. Epub 2020 Aug 7. PMID: 32771461; PMCID: PMC7410805; McCullough PA, Alexander PE, Armstrong R, et al., *Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)*. Rev Cardiovasc Med. 2020 Dec 30;21(4):517-530. doi: 10.31083/j.rcm.2020.04.264. PMID: 33387997.

[77] Kory, Pierre MD, Meduri, Gianfranco Umberto MD; Varon, Joseph MD; Iglesias, Jose DO; Marik, Paul E. MD, *Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin*

144. In Africa, Ivermectin is given once or twice yearly to prevent river blindness, and chloroquine or Hydroxychloroquine is taken once weekly to prevent malaria. Thus, they function like vaccines when used in advance of exposure. Rates of COVID-19 cases and deaths in Africa have turned out to be only a small fraction of what they are in the US.[78]

145. Many countries and regions have been administering over the counter Ivermectin for COVID with excellent reported treatment success.

146. The probable efficacy of chloroquine drugs for coronaviruses was demonstrated in experiments published by the CDC in 2005 and by Dr. Fauci's National Institute of Allergy and Infectious Diseases (NIAID) in 2014.[79] This prior knowledge, obtained by CDC and NIH regarding these drugs' efficacy at standard doses and their safety at standard doses, while agency officials suppressed their use during the pandemic, is clear evidence of willful misconduct and should nullify liability protection for these federal officials.

147. In addition, these two inexpensive, readily available drugs are effective regardless of viral variant or strain, and their effects, used weekly, do not wear off after a few months, requiring additional booster shots with possible side effects.

148. Yet, the FDA has exhibited bias regarding the effective and safe use of such alternatives,

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in the Prophylaxis and Treatment of COVID-19, AMERICAN JOURNAL OF THERAPEUTICS, May/June 2021 - Volume 28 - Issue 3 - p e299-e318, https://journals.lww.com/americantherapeutics/Fulltext/2021/06000/Review_of_the_Emerging_Evidence_Demonstrating_the.4.aspx.

[78] Guerrero R, Bravo LE, Muñoz E, Ardila EKG, Guerrero E. COVID-19: The Ivermectin African Enigma. Colomb Med (Cali). 2020 Dec 30;51(4):e2014613. doi: 10.25100/cm.v51i4.4613; Hisaya Tanioka, Sayaka Tanioka, Kimitaka Kaga, *Why COVID-19 is not so spread in Africa: How does Ivermectin affect it?,* Europe PMC 2021 Mar 26. doi: https://doi.org/10.1101/2021.03.26.21254377.

[79] Martin J Vincent, Eric Bergeron, et al., *Chloroquine is a potent inhibitor of SARS coronavirus infection and spread,* BMC Virology Journal (August 22, 2005), available at https://doi.org/10.1186/1743-422X-2-69.

denying their effectiveness and failing to consider them as a viable, and potentially preferential, method to alleviate severe disease and death, nullifying the need for any vaccination scheme. Not only that, but they have also encouraged the vilification of such resources.

149. Many medical professionals suspect FDA's feigned ignorance about Ivermectin was a prerequisite to issuing EUAs for COVID vaccines, given the EUA requirement that no approved drug be available for the same indication.

150. If children and adults were treated early with proven drug combinations, very few would progress to the inflammatory and thrombotic stages of COVID-19. While this statement may appear controversial, forest plots of the compiled literature on Hydroxychloroquine and Ivermectin for COVID are very compelling, with average efficacy against the different endpoints of 64% to over 80%.

151. There is no COVID-19 emergency for children aged 5-11. There are safer drugs that could be used prophylactically and therapeutically for COVID in children. There is extensive and compelling medical evidence for this assertion; and FDA's decision to eschew use of these drugs in favor of a demonstrably dangerous vaccine is arbitrary and capricious.

152. The law on "authorization for medical products for use in emergencies" requires that the EUA designation be used only when "**there is no adequate, approved, and available alternative** to the product for diagnosing, preventing, or treating such disease or condition." 21 U.S.C. § 360bbb-3(3) (emphasis added).

153. Recognizing and approving Hydroxychloroquine, Ivermectin, and other successful alternative treatments would have prevented COVID-19 biologics from receiving any emergency use authorization. As such, the FDA's revocation of the EUA for chloroquine

phosphate and Hydroxychloroquine for use on COVID-19 patients was a de facto attempt to stop doctors prescribing and treating patients with it, to ensure that the path was clear to grant EUAs for these so-called vaccines.[80]

CAUSE OF ACTION I:
VIOLATION OF THE ADMINISTRATIVE PROCEDURES ACT

154. Plaintiffs incorporate the foregoing paragraphs as if fully set forth herein.

155. The Administrative Procedures Act (APA) requires "[e]ach agency [to] give an interested person the right to petition for the issuance, amendment, or repeal of a rule." 5 U.S.C. § 553(e).

156. The APA does not set fixed timelines for agency action and, instead, requires agency action within a "reasonable" time by providing judicial review to "compel agency action unlawfully withheld or *unreasonably delayed*." 5 U.S.C. § 706(2). A "reasonable time for agency action is typically counted in weeks or months, not years," *In re Am. Rivers & Idaho Rivers United*, 372 F.3d 413, 419 (D.C. Cir. 2004), and an agency action's exigent context may demand expedited review. *Fund for Animals v. Norton*, 294 F.Supp.2d 92, 114 (D.D.C. 2003) ("pressing human health concerns…demand prompt review").

157. Congress requires that courts "shall hold unlawful and set aside" any agency "action," "finding," or "conclusion" whenever the agency failed to follow the necessary process for reasoned decision-making. 5 U.S.C. § 706(2)(A). The traditional judicial protocol is to vacate the agency action and remand the matter to the agency for compliance with the requisite process before taking any further action.

[80] *Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine,* U.S. Food & Drug Administration, available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.

158. The Administrative Procedures Act protects the public from arbitrary and capricious executive branch action by imposing the rule of reason and the rule of law through judicial oversight. An agency is "required to engage in reasoned decision making." *Michigan v. EPA*, 576 U.S. 743, 750 (2015). This requires that the agency "examine the relevant data." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). This also requires that the agency "articulate a satisfactory explanation for its action." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). An agency action is considered "arbitrary and capricious" if it fails to comply with the rules of reason articulated in *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

The FDA abused its power under the emergency use statute

159. The emergency use authorization statute, which allows the FDA to authorize emergency drugs without going through the formal, comprehensive approval process, and under which the FDA has authorized the use of the COVID-19 vaccine for children ages 5-16, requires that an actual emergency exist. This is an essential prerequisite to a loophole that removes barriers to approval that are in place to ensure safety and effectiveness.

160. This is a high burden to meet, as evidenced by the fact that an EUA has *never* been previously granted for a brand-new vaccine. The only vaccine to have been authorized for emergency use was AVA, an anthrax vaccine, which had already been formally approved by the FDA for other purposes.[81]

[81] Jonathan Iwry, *From 9/11 to COVID-19: A Brief History of FDA Emergency Use Authorization,* Harvard Law Petrie-Flom Center (January 28, 2021), available at https://blog.petrieflom.law.harvard.edu/2021/01/28/fda-emergency-use-authorization-history/.

161. To support an EUA declaration, certain circumstances must exist to justify the authorization. § 564(b)(1). As the FDA admits, "a determination under section 319 of the Public Health Service Act that a public health emergency exists, such as the one issued on January 31, 2020, does not enable FDA to issue EUAs."[82]

162. The FDA here has failed to justify its conclusion that children ages 5-11 face an emergency that warrants subjecting them to life-threatening short-term adverse effects, and untold long-term adverse effects.

163. Young children are the *least* at risk from SARS-CoV-2. Children that do contract COVID-19 typically do not become as sick as adults, with most children having mild or no symptoms.[83] Those few that have experienced severe symptoms or death from COVID-19 have almost exclusively had comorbidities or other underlying health conditions.[84] The survival rate of children who have tested positive for COVID-19 is exceptionally high.

164. Even assuming that children are at risk from SARS-CoV-2, given that the Pfizer-BioNTech COVID-19 biologic has only been marginally effective at reducing severe symptoms hospitalization, or death, which children ages 5-11 are not highly susceptible to, and ineffective at reducing transmission, which children are affected by, it is medically unnecessary for children to receive this biologic.

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[82] *Emergency Use Authorization,* U.S. Food & Drug Administration (December 3, 2021), available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

[83] *COVID-19 (coronavirus) in babies and children,* Mayo Clinic, available at https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-in-babies-and-children/art-20484405.

[84] Clare Smith, David Odd, Rachel Harwood, et al., *Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: a national study using linked child death reporting data,* Research Square (July 7, 2021), DOI: 10.21203/rs.3.rs-689684/v1, available at https://www.researchsquare.com/article/rs-689684/v1.

165. Meanwhile, the adverse effects from the COVID-19 biologic that have been witnessed in children can be serious and deadly. The FDA has failed to properly address these risks and are still analyzing them through clinical trials that are not scheduled to be completed until this drug has been marketed to young children for several years.

166. As the risk of COVID-19 to children 5-11 cannot be categorized as an emergency, the FDA is not at liberty to utilize the emergency use authorization statute to carry out their agenda of putting this Pfizer biologic in the arms of every American, no matter the cost.

The FDA was not entitled to use its emergency powers on the grounds that Congress failed to conduct its six-month review of national emergencies

167. The National Emergencies Act (NEA) is intended to provide the executive with flexibility and unique powers in dire and urgent times. Congress, however, is ordered to provide a check and balance on the executive's emergency powers to prevent a potential abuse of authority.

168. The FDA has based its emergency authorization authority, in part, upon the declaration of a national emergency.

169. 50 U.S.C. § 1622, which addresses the termination of national emergencies, requires that "[n]ot later than six months after a national emergency is declared, and not later than the end of each six-month period thereafter that such emergency continues, each House of Congress shall meet to consider a vote on a joint resolution to determine whether that emergency shall be terminated." 50 U.S.C. § 1622(b).

170. More than a year after the COVID-19 national emergency was declared on March 13, 2020 by President Trump, Congress had still not met to consider whether the COVID-19 emergency should continue. In May 2021, several representatives introduced a joint

resolution to terminate the COVID-19 emergency declared under the National Emergencies Act (NEA).[85] This joint resolution was never voted on, nor was another joint resolution ever introduced.

171. Congress has failed to perform its function as a safeguard against this abuse of power. The national emergency declaration is not set to expire until March 1, 2022, nearly two years after the initial designation with no checks and balances.

172. It is within this culture of an unmitigated "national emergency" that the Defendant agency has taken extreme and unauthorized liberties to deliver COVID-19 vaccines to the public, no matter the consequences or the number of victims of such activity.

173. Defendants capitalized upon this national emergency declaration to provide an excuse for their grift against the American people.

The FDA denied CHD its procedural right to seek redress via citizen petition, a right conforming to the right to petition under the First Amendment.

174. The First Amendment guarantees the right to petition one's government and the necessity of robust debate following strict scientific standards.

175. "A private citizen exercises a constitutionally protected First Amendment right anytime he or she petitions the government for redress." *Fregia v. Bright*, No. 1:16-CV-187, 2017 U.S. Dist. LEXIS 179667, *11 (E.D. Tex. Aug. 15, 2017). Citizens are guaranteed by the First Amendment "the right of access to all branches of the government for the redress of wrongs." *Noles v. Dial*, No. 3:20-CV-3677-N-BK, 2021 U.S. Dist. LEXIS 178694, *17 (N.D. Tex. Aug. 25, 2021).

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[85] *Gosar Introduces Joint Resolution to Terminate the COVID-19 Emergency Declaration,* May 20, 2021, available at https://gosar.house.gov/news/email/show.aspx?ID=N5POWQSNCMBCEN7YPCI4Z4PJIU.

176. Plaintiff CHD exercised that right by filing a citizen petition on May 16, 2021, which garnered more than 30,000 comments from individuals, requesting that the FDA halt the licensing of COVID-19 until such time as the concerns outlined in the petition be alleviated and the proper scientific and administrative processes be followed.

177. Defendants failed to adequately address the concerns in their response, which was delivered on the same day that the Pfizer "Comirnaty" vaccine received its official approval. Defendants' response did nothing to ameliorate the legitimate and grave grievances presented in the petition.

178. This latest in the series of EUAs that Defendants have granted, this time aimed at young children who are least at risk from COVID-19, is a continuation of the violative and harmful actions Defendants have taken in their promotion of the COVID-19 Pfizer biologic.

179. Unless and until Defendants properly allow for citizen engagement, follow the laws governing their role as an administrative agency, and address the underlying concerns presented by Plaintiff CHD in the original citizen petition, Defendants unbridled contempt for the rights of citizens guaranteed by the Constitution and their resulting illegal wielding of power over the public's health must be stopped.

The FDA redefined the term "vaccine" in violation of procedural due process,

180. The FDA and CDC have altered the traditional definitions of "Vaccine" and "Vaccination" to encompass the COVID-19 biologics and have the ability to market and administer them as vaccines, although they do not fit the century-long definition of the word.

181. Defendants failed to provide a citizen participation or notice-and-comment process when it labeled the COVID-19 biologics as vaccines. This erroneous labelling has misled the

public and created an unfounded trust in the biologic. By promoting it as a "vaccine," which comes with a connotation of a medical miracle, rather than its true label of an experimental pharmaceutical gene therapy, Defendants have been able to propagate a national vaccination campaign based on the public's erroneous beliefs.

182. Plaintiffs Deborah L. Else and Sacha Dietrich, on behalf of their children, and CHD, on behalf of their members, have themselves felt the harm that has come from this false designation through the mass vaccination scheme, as well as the pressure, coercion and discrimination that has resulted.

Mislabeling the Drug & Marketing it to Children

183. Defendants marketed this emergency use only drug to children as if it were a biologic licensed drug, failing to follow restrictions on marketing biologics to children, or in general, without disclosing it does not fit the traditional and historic medical definition of a vaccine, without disclosing any fair balance between risks and efficacy, and without disclosing the very low risks of the disease the drug "treats" for children.

184. Plaintiffs are directly affected by the advertisements and societal pressures encouraging their children to receive the COVID-19 Pfizer-BioNTech biologic.

185. The FDA's illegal actions have encouraged people in positions of authority to push this experimental biologic on our nation's youth. Plaintiff Deborah Else attests to recommendations by her children's school to receive the Pfizer BioNTech biologic, which is available at vaccine clinics provided on school grounds. Pediatricians have also sent notices to parents encouraging vaccination, despite the almost zero risk of serious symptoms or death in children who contract COVID-19. This societal push toward vaccination has

culminated in an inundation of pro-vaccine messaging; advertisements on television, radio shows, announcements and signage in stores, and even the manipulation of popular children's characters such as Sesame Street's Big Bird have been employed to propagandize the public and the youth.

186. Plaintiff Sacha Dietrich attests that because of FDA's unlawful EUA, her children are constantly harassed by directives to receive the COVID-19 biologic and are continuously pressured by the media and other children.

Defendants Failed to Articulate Any Standard for Assessing Risk

187. This agency process requires Defendants to articulate a clear standard for assessing the safety, efficacy, and necessity of any drug or biologic, whether for an EUA or license. This is especially so when the product is likely to be mandated to millions of people around the world. *Burlington Truck Lines v. United States*, 371 U.S. 156, 158 (1962). This also requires that the agency "articulate a satisfactory explanation for its action." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

188. The FDA failed to articulate any standard for assessing an individualized, stratified risk for children between the ages of 5 and 11 from the various vaccines, including any risk assessment specific to the variants of the virus, the efficacy of the vaccines to variants of the virus, or the risks of the vaccines themselves by any statistical measurement to children in that age group. The FDA's failure violated their obligation to make such a standard, provide the individualized, stratified analysis, and give some measurable assessment for children, and their parents, to assess the risks of each option for themselves.

189. This is further demonstrated by the documented fraud in Pfizer's clinical trials, of which

Defendants were fully aware and refused to investigate. Defendants turned a blind eye to falsified data, ignoring adverse reported adverse events, failing to follow protocols, revealing confidential participant information, and adverse actions taken against staff who spoke out against these issues. As such, without a widespread investigation into Pfizer's clinical trial practices, Defendants have failed to explain how and why their findings from these studies should be relied upon in order to justify the issuance of EUAs for children aged 5-11 and how their risk assessment is accurate.

190. Since the launch of the first COVID-19 biologic in 2020, the FDA's method for assessing risk for all individuals, but especially children aged 5-11, has been wholeheartedly inadequate and is still shrouded in mystery.

191. The FDA also failed to examine and regulate mRNA COVID-19 vaccines as gene therapies. The failure to apply these required criteria, which are more stringent than the criteria the FDA applies to vaccines generally and the complete lack of an assessment standard for these gene therapies in FDA's EUA assessment, is arbitrary and capricious.

Defendants failed to Examine Relevant Data

192. As part of "reasoned decision making," an agency is required to "examine the relevant data." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983)

193. Defendant failed to address the inadequacies regarding its clinical trials. Scientists from other countries readily acknowledge that "[c]linical trials for these inoculations were very short-term (a few months), had samples not representative of the total population, and for adolescents/children, had poor predictive power because of their small size. Most

importantly, the clinical trials did not address long-term effects that, if serious, would be borne by children/adolescents for potentially decades."[86]

194. In addition, the FDA ignores the fact that "[t]he bulk of the official COVID-19 attributed deaths per capita occur in the elderly with high comorbidities, and the COVID-19 attributed deaths per capita are negligible in children."[87] Children don't need these vaccines. The argument that children must risk their health to protect adults is completely unethical if not evil. Children and adolescents tend to have milder symptoms compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them. The FDA cannot grant an emergency use authorization when there is no emergency for this age group.

195. The FDA's proclivity to curry favor to pharmaceutical companies under a thinly veiled guise of protecting children is painfully obvious. The statistics are clear, healthy children have a miniscule risk of contracting COVID-19. What's more, the mortality rate in children is negligible, and many are thought to have had COVID-19, providing them with natural immunity anyway. In fact, nearly half of all children have natural immunity to COVID, according to the CDC.

196. Defendants have furthermore ignored adverse events that have been documented through the VAERS database, despite the fact that the input of event reports to VAERS since the COVID vaccines were rolled out is greater than all cumulative adverse event reports to

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[86] *Why are we vaccinating children against COVID-19?,* Science Direct, available at https://www.sciencedirect.com/science/article/pii/S221475002100161X?via%3Dihub.

[87] Kostoff RN, Calina D, Kanduc D, Briggs MB, Vlachoyiannopoulos P, Svistunov AA, Tsatsakis A. *Why are we vaccinating children against COVID-19?* Toxicol Rep. 2021;8:1665-1684. doi: 10.1016/j.toxrep.2021.08.010. Epub 2021 Sep 14. Erratum in: Toxicol Rep. 2021 Oct 7;: PMID: 34540594; PMCID: https://pubmed.ncbi.nlm.nih.gov/34540594/.

VAERS for the prior thirty years. The failure to investigate this fact before administering this experimental injection to our nation's children goes beyond arbitrary and capricious action; it is amoral.

197. Meanwhile, Defendants have dismissed the effectiveness of alternative treatments, which have the potential to significantly reduce hospitalizations and death to the extent that any vaccination program may have been wholly unnecessary. Such treatments, had they been recognized by the FDA, would have threatened the agency's ability to issue EUAs.

198. Defendants' hype is outweighed by tidbits of truth that the public is forced to ferret out from an ever-increasingly censored media. These experimental and prematurely licensed vaccines are not only dangerous and defective, but their efficacy has also been grossly exaggerated. There is substantial evidence that vaccine effectiveness wanes substantially after only six months, hence the narrative that booster shots are necessary for remaining protected, which Defendants have ignored. Defendants have willfully ignored data critical of the Pfizer biologic, opening up children to be victims of a consistent schedule of COVID-19 injections that are inadequately tested and, based on empirical evidence, potentially dangerous. In so doing, Defendants have demonstrated that they are willing to arbitrarily and capriciously gamble with the lives of tens or hundreds of millions of children.

199. Dr. Eric Ruben, an advisory committee member to the FDA, said this about the COVID vaccine in children 5-11 during an official FDA hearing: "We're never going to learn about how safe the vaccine is until we start giving it. That's just the way it goes."[88]

[88] *FDA Panelist on Vaccinating 5-year-olds: "We're never going to learn about how safe the vaccine is until we start giving it,"* 93.1FMWIBC (October 27, 2021) available at https://www.wibc.com/blogs/mock-n-rob/fda-panelist-on-vaccinating-5-year-olds-were-never-going-to-learn-about-how-safe-the-vaccine-is-until-we-start-giving-it/.

200. CDC's Acting Director Dr. Rochelle Walensky stated, on the one hand "Our vaccines are working exceptionally well. . ." She clarifies with "They continue to work well for Delta, with regard to severe illness and death – they prevent it. But what they can't do anymore is prevent transmission."[89]

201. This lawsuit simply asks the FDA to follow its own rules and hit the pause button on this pedicide, this rush to pharmapocalypse. It seeks vacatur of the authorization for children aged 5-11, as well as remand for the Defendants to abide by their legal obligations, statutory duties, and scientific processes.

202. The FDA has failed to engage in a pluralistic, critical, open, transparent, and scientific dialogue with the public based on careful, deliberative evaluation of all relevant research and experience since it authorized COVID-19 vaccines. On the contrary, it recklessly rushed the Pfizer- BioNTech COVID-19 biologic authorization without proper evaluation in violation of the APA.

203. Plaintiffs bring this action because the FDA is failing to carry out its mission and is once again shamelessly displaying its true colors as a captured agency that ignores health and safety while granting favors to pharma. Plaintiffs seek this Court's intervention to put the FDA back on the path to lawful protection of the public in these precarious times.

204. Defendants' arbitrary and capricious actions warrant a stay, a vacatur and remand.

CAUSE OF ACTION II: DECLARATORY RELIEF

205. Plaintiffs incorporate the foregoing paragraphs as if fully set forth herein.

206. Plaintiffs seek a declaratory judgment that the defendants cannot use the emergency

[89] Vaccines fail to prevent transmission, The Situation Room Twitter, available at https://twitter.com/CNNSitRoom/status/1423422301882748929.

authorization statute to mislabel drugs as vaccines, mislabel drugs that have not been thoroughly tested as safe and effective, mislabel drugs as permitted to be compelled without informed consent, and to mislabel drugs to children that result in mandates being issued concerning those children's access to basic services, including medical and educational services, rather than the regular biologic licensure process which incorporates citizen participation provisions, including the right of a citizen petition and response thereto.

207. Congress expressly created this remedy of declaratory relief for federal courts as a critical check on the abuse of power by an executive branch agency, and thereby authorize by law that this Court "may declare the rights and other legal relations of ay interested party seeking such declaration." 28 U.S.C. § 2201.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff s Children's Health Defense, Deborah L. Else, and Sacha Dietrich respectfully ask this Court:

i. To enjoin any further marketing or promotion of the drug to children, to stay the FDA's decision to grant Emergency Use Authorization for Pfizer-BioNTech's COVID-19 vaccine for children aged 5-11, and to vacate and remand the decision to the agency;

ii. To award attorneys' fees and costs, as authorized under 28 U.S.C. § 2412; and

iii. To grant all other appropriate relief as necessary.

Dated: January 24, 2022

Respectfully submitted,

/s/ Robert E. Barnes
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Counsel for Plaintiffs CHILDREN'S HEALTH DEFENSE, Deborah L. Else, and Sacha Dietrich.

Exhibit 1

FDA NEWS RELEASE

FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age

For Immediate Release:

October 29, 2021

Español (/news-events/press-announcements/la-fda-autoriza-vacuna-contra-el-covid-19-de-pfizer-biontech-para-uso-de-emergencia-en-ninos-de-5-11)

Today, the U.S. Food and Drug Administration authorized the emergency use of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 to include children 5 through 11 years of age. The authorization was based on the FDA's thorough and transparent evaluation of the data that included input from independent advisory committee experts who overwhelmingly voted in favor of making the vaccine available to children in this age group.

Key points for parents and caregivers:

- Effectiveness: Immune responses of children 5 through 11 years of age were comparable to those of individuals 16 through 25 years of age. In addition, the vaccine was found to be 90.7% effective in preventing COVID-19 in children 5 through 11.
- Safety: The vaccine's safety was studied in approximately 3,100 children age 5 through 11 who received the vaccine and no serious side effects have been detected in the ongoing study.
- The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (https://www.cdc.gov/vaccines/acip/index.html) will meet next week to discuss further clinical recommendations.

"As a mother and a physician, I know that parents, caregivers, school staff, and children have been waiting for today's authorization. Vaccinating younger children against COVID-19 will bring us closer to returning to a sense of normalcy," said Acting FDA Commissioner Janet Woodcock, M.D. "Our comprehensive and rigorous evaluation of the data pertaining to the vaccine's safety and effectiveness should help assure parents and guardians that this vaccine meets our high standards."

The Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age is administered as a two-dose primary series, 3 weeks apart, but is a lower dose (10 micrograms) than that used for individuals 12 years of age and older (30 micrograms).

In the U.S., COVID-19 cases in children 5 through 11 years of age make up 39% of cases in individuals younger than 18 years of age. According to the CDC, approximately 8,300 COVID-19 cases in children 5 through 11 years of age resulted in hospitalization. As of Oct. 17, 691 deaths from COVID-19 have been reported in the U.S. in individuals less than 18 years of age, with 146 deaths in the 5 through 11 years age group.

"The FDA is committed to making decisions that are guided by science that the public and healthcare community can trust. We are confident in the safety, effectiveness and manufacturing data behind this authorization. As part of our commitment to transparency around our decision-making, which included our public advisory committee meeting earlier this week, we have posted documents today supporting our decision and additional information detailing our evaluation of

the data will be posted soon. We hope this information helps build confidence of parents who are deciding whether to have their children vaccinated," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research.

The FDA has determined this Pfizer vaccine has met the criteria for emergency use authorization. Based on the totality of scientific evidence available, the known and potential benefits of the Pfizer-BioNTech COVID-19 vaccine in individuals down to 5 years of age outweigh the known and potential risks.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the EUA in children down to 5 years of age is based on an ongoing randomized, placebo-controlled study that has enrolled approximately 4,700 children 5 through 11 years of age. The study is being conducted in the U.S., Finland, Poland and Spain. Children in the vaccine group received two doses of the Pfizer-BioNTech COVID-19 Vaccine containing 10 micrograms of messenger RNA per dose. The FDA analyzed data that compared the immune response of 264 participants from this study to 253 participants 16 through 25 years of age who had two higher doses of the vaccine in a previous study which determined the vaccine to be effective in preventing COVID-19. The immune responses of the younger age participants were comparable to the older participants.

The FDA also conducted a preliminary analysis of cases of COVID-19 occurring seven days after the second dose. In this analysis, among participants without evidence of prior infection with SARS-CoV-2, 3 cases of COVID-19 occurred among 1,305 vaccine recipients and 16 cases of COVID-19 occurred among 663 placebo recipients; the vaccine was 90.7% effective in preventing COVID-19.

FDA Evaluation of Available Safety Data

The available safety data to support the EUA include more than 4,600 participants (3,100 vaccine, 1,538 placebo) ages 5 through 11 years enrolled in the ongoing study. In this trial, a total of 1,444 vaccine recipients were followed for safety for at least 2 months after the second dose.

Commonly reported side effects in the clinical trial included injection site pain (sore arm), redness and swelling, fatigue, headache, muscle and/or joint pain, chills, fever, swollen lymph nodes, nausea and decreased appetite. More children reported side effects after the second dose than after the first dose. Side effects were generally mild to moderate in severity and occurred within two days after vaccination, and most went away within one to two days.

The FDA and CDC safety surveillance systems have previously identified increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of tissue surrounding the heart) following vaccination with Pfizer-BioNTech COVID-19 Vaccine, particularly following the second dose, and with the observed risk highest in males 12 through 17 years of age. Therefore, the FDA conducted its own benefit-risk assessment using modelling to predict how many symptomatic COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths from COVID-19 the vaccine in children 5 through 11 years of age would prevent versus the number of potential myocarditis cases, hospitalizations, ICU admissions and deaths that the vaccine might cause. The FDA's model predicts that overall, the benefits of the vaccine would outweigh its risks in children 5 through 11 years of age.

Ongoing Safety Monitoring

Pfizer Inc. has updated its safety monitoring plan to include evaluation of myocarditis, pericarditis and other events of interest in children 5 through 11 years of age. In addition, the FDA and the CDC have several systems in place to continually monitor COVID-19 vaccine safety and allow for the rapid detection and investigation of potential safety problems.

It is mandatory for Pfizer Inc. and vaccination providers to report to any serious adverse events, cases of Multisystem Inflammatory Syndrome and cases of COVID-19 that result in hospitalization or death in vaccinated individuals. It is also mandatory for vaccination providers to report all vaccine administration errors to VAERS for which they become aware and for Pfizer Inc. to include a summary and analysis of all identified vaccine administration errors in monthly safety reports to the FDA.

Data Supports New Vaccine Formulation to Improve Stability and Storage Conditions

The FDA today also authorized a manufacturing change for the vaccine to include a formulation that uses a different buffer; buffers help maintain a vaccine's pH (a measure of how acidic or alkaline a solution is) and stability. This new formulation is more stable at refrigerated temperatures for longer periods of time, permitting greater flexibility for vaccination providers.

The new formulation of the vaccine developed by Pfizer Inc. contains Tris buffer, a commonly used buffer in a variety of other FDA-approved vaccines and other biologics, including products for use in children. The FDA evaluated manufacturing data to support the use of Pfizer-BioNTech COVID-19 Vaccine containing Tris buffer and concluded it does not present safety or effectiveness concerns.

Related Information

- Pfizer-BioNTech COVID-19 Vaccine (/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine)
- COVID-19 Vaccines (/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines)
- Emergency Use Authorization for Vaccines Explained (/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained)

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The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Inquiries

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FDA Office of Media Affairs (mailto:fdaoma@fda.hhs.gov)

301-796-4540

Consumer:

888-INFO-FDA

More Press Announcements (/news-events/newsroom/press-announcements)

Exhibit 2

Children's Health Defense

May 16, 2021

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Acting Commissioner Janet Woodcock, M.D.
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Acting Commissioner Woodcock:

Enclosed is a Citizen Petition filed on behalf of Children's Health Defense by Meryl Nass, M.D., Scientific Advisory Board member, and Robert F. Kennedy, Jr., Board Chair and Chief Litigation Counsel, requesting that the FDA revoke Emergency Use Authorizations for existing COVID vaccines and refrain from approving and licensing them.

Dr. Nass and Mr. Kennedy look forward to your timely review of this petition. They are available to answer questions and to provide any additional relevant information.

Sincerely yours,

Mary Holland
President and General Counsel
(845) 445-7807
mary.holland@childrenshealthdefense.org

VIA ELECTRONIC FILING

May 16, 2021

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION REGARDING COVID-19 VACCINES	Docket No. _____

CITIZEN PETITION

On behalf of Children's Health Defense, the undersigned submit this petition under 21 C.F.R. § 10.20, § 10.30, § 50.23, § 600 – 680, § 601.2; 10 U.S.C. § 1107(f), § 1107a; 21 U.S.C. § 355(i)(4), § 360bbb-3; 42 U.S. Code § 247d; § 564 of the Federal Food, Drug, and Cosmetic Act (FDCA); the Public Readiness and Emergency Preparedness Act; the Public Health Service Act, and § 553(e) of the Administrative Procedures Act.

We request the Acting Commissioner of the Food and Drugs Administration (FDA) to issue, amend, revoke, or refrain from taking the administrative actions listed below regarding emergency use authorizations (EUAs), current and future new drug applications (NDAs), and biologics license applications (BLAs) for all COVID vaccines.

I. ACTIONS REQUESTED

1. FDA should revoke all EUAs and refrain from approving any future EUA, NDA or BLA for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs.

2. Given the extremely low risk of severe COVID illness in children, FDA should immediately refrain from allowing minors to participate in COVID vaccine trials, refrain from amending EUAs to include children, and immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines.

3. FDA should immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect.

4. FDA should immediately amend its existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID, to comport with current scientific evidence of safety and efficacy at currently used doses and immediately issue notifications to all stakeholders of this change.

5. The FDA should issue guidance to the Secretary of the Defense and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers under 10 U.S.C. § 1107(f) or 10 U.S.C. § 1107a.

6. The FDA should issue guidance to all stakeholders in digital and written formats to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences, under 21 U.S.C. § 360bbb-3(e)(1)(a)(ii)(III) [1] and the informed consent requirements of the Nuremberg Code.[2]

7. Pending revocation of COVID vaccine EUAs, FDA should issue guidance that all marketing and promotion of COVID vaccines must refrain from labeling them "safe and effective," as such statements violate 21 U.S.C. § 360bbb-3.

II. STATEMENT OF GROUNDS

A. Safety

8. Vaccine Adverse Event Reporting System (VAERS) data reveal unprecedented levels of deaths and other adverse events since the FDA issued Emergency Use Authorizations (EUAs) for three COVID vaccines. As of May 10, 2021, VAERS reported 4,434 deaths of people who received at least one COVID vaccination.[3]

9. FDA and CDC have not responded to these data by issuing any warnings or restricting the use of these vaccines. Furthermore, the VAERS database is the only safety database to which the public has access. The government withholds extensive safety information from the public despite having at least ten additional data sources and expert consultants to analyze these data, according to Nancy Messonier, MD, the Director of the National Center for Immunization and Respiratory Diseases.[4] Examples include databases from the Centers for Medicare and

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[1] 21 U.S.C. § 360bbb-3, Authorization for medical products for use in emergencies, https://www.govinfo.gov/content/pkg/USCODE-2011-title21/pdf/USCODE-2011-title21-chap9-subchapV-partE-sec360bbb-3.pdf.

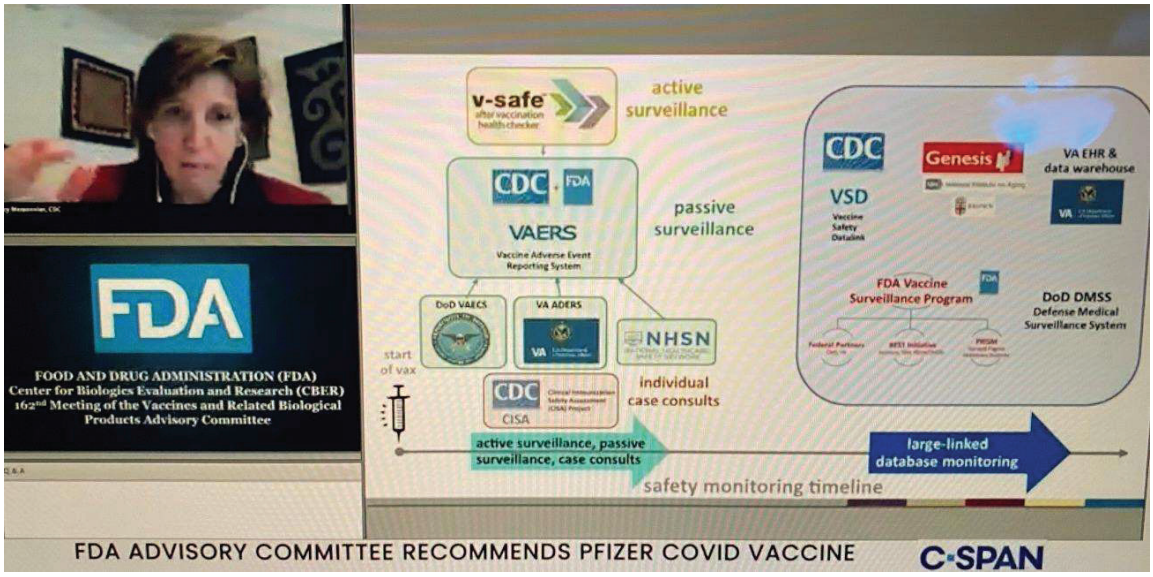
[2] Nuremburg Code, BRITISH MEDICAL JOURNAL, No. 7070, Volume 313, p. 1448 (Dec. 7, 1996), https://media.tghn.org/medialibrary/2011/04/BMJ_No_7070_Volume_313_The_Nuremberg_Code.pdf.

[3] VAERS Vaccine Adverse Event Reporting System data, available at https://vaers.hhs.gov/.

[4] FDA meeting on COVID 19 and Emergency Use Authorization, Part 1 (Video), Dec. 10, 2020, available at https://www.c-span.org/video/?507053-1/fda-meeting-covid-19-vaccine-emergency-authorization-part-1.

Medicaid, the Veterans Administration, the Defense Department (DMSS), the Vaccine Safety Datalink and the "Genesis" database, which is operated in cooperation with the National Institutes of Health and Brown University and includes 250 long-term care facilities and 35,000 residents.

10. Dr. Messonier told the FDA and its Vaccines and Related Biological Products Advisory Committee (VRBPAC) on December 10, 2020 that it had 11 systems that would evaluate COVID vaccine safety. Five systems would be active at the start of the vaccine program, and an additional six systems would become active over ensuing weeks. She said that the VAERS system was being enhanced for long-term care facilities, and added, "Hopefully you'll understand how robust these systems are." Below is the graphic she presented to the VRBPAC and the public on December 10, 2020.



11. The CDC website, updated on May 11, 2021 states, "These vaccines have undergone and will continue to undergo the most intensive safety monitoring in U.S. history. This monitoring includes using both established and new safety monitoring systems to make sure that COVID-19 vaccines are safe."[5]

12. The CDC website states that "CDC and FDA physicians review each case report of death as soon as notified and CDC requests medical records to further assess reports."[6] By contrast, a CDC official told a reporter for *The Daily Beast* that it lacks a "good way to track deaths that occur after vaccination in real time." Furthermore, CDC told the reporter, "there are no current plans to include vaccination data in the current CDC Covid-19 mortality analysis."[7]

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[5] CDC, *Safety of COVID-19 Vaccines* (updated May 11, 2021), https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/safety-of-vaccines.html.

[6] CDC, *Selected Adverse Events Reported after COVID-19 Vaccination* (updated May 11, 2021), https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

[7] Erin Banco, *White House asks CDC to study how many have died after COVID vaccine shots*,

13. Children's Health Defense asked CDC for information on post-vaccination deaths and injuries in early March 2021 and has yet to receive a response.[8]

14. Normally, licensed biologics manufacturers review adverse event reports pursuant to 21 C.F.R. § 600.80, while to date the CDC and the manufacturers appear to dispute most causal links to COVID vaccines. Any COVID vaccine license applicant "assumes responsibility for compliance with the applicable product and establishment standards" according to 21 C.F.R. § 600.3.[9] CDC asserts that a "review of available clinical information, including death certificates, autopsy, and medical records has not established a causal link to COVID-19 vaccines," yet recent assessments acknowledge "a plausible causal relationship between the J&J/Janssen COVID-19 vaccine and a rare and serious adverse event—blood clots with low platelets—which has caused deaths."[10] Denmark, among other nations, has banned the EUA J&J/Janssen COVID vaccine, stating, "the benefits of using the COVID-19 vaccine from J&J do not outweigh the risk of causing possible adverse effect in those who receive the vaccine."[11]

15. CDC calculated rates of adverse effects for anaphylaxis post-vaccination improperly, using VAERS reports as the numerator, even though CDC officials have acknowledged "it is not possible to use VAERS data to calculate how often an adverse event occurs in a population."[12] When Massachusetts General-Brigham hospitals evaluated the rate of anaphylaxis in employees post COVID vaccination, they found anaphylaxis rates approximately 50-100 times greater than the rates CDC calculated using VAERS data. (Pfizer rate 2.7/10,000 vaccinees and Moderna rate 2.3/10,000 vaccinees).[13] Anaphylaxis after vaccination has led to deaths. If this degree of underestimation holds true for other adverse events using the VAERS database, then the safety of COVID vaccines is considerably worse than it currently appears. This rate could be verified by querying the ten databases whose results have been hidden from the

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DAILY BEAST (Jan. 28, 2021), https://www.thedailybeast.com/white-house-asks-cdc-to-study-how-many-have-died-after-covid-vaccine-shots.

[8] Megan Redshaw, *64 Days and Counting — Why Won't the CDC Answer Our Questions?* THE DEFENDER (May 11, 2021), https://childrenshealthdefense.org/defender/64-days-why-wont-cdc-answer-questions/.

[9] Code of Federal Regulations Title 21 § 600.3, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3.

[10] CDC, *Selected Adverse Events Reported after COVID-19 Vaccination* (updated May 11, 2021), https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

[11] Vincent West, *Denmark ditches J&J COVID-19 shots from vaccination programme*, REUTERS (May 3, 2021), https://www.reuters.com/world/europe/denmark-excludes-jj-shot-vaccine-programme-local-media-reports-2021-05-03/.

[12] CDC, Vaccine Adverse Event Reporting System (VAERS), https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html.

[13] Blumenthal K. G., Robinson L. B., Camargo C. A., et al., *Acute Allergic Reactions to mRNA COVID-19 Vaccines*. JAMA, Vol. 325, No. 15, pp. 1562–1565 (Mar. 8, 2021), https://jamanetwork.com/journals/jama/fullarticle/2777417.

public.

16. Other problems with vaccine safety assessment may exist because of inadequate animal toxicology and pharmacokinetic studies of COVID vaccines. Animal experiments failed to measure the quantity, duration and organ distribution of spike protein production. The animal experiments, incomprehensibly, failed to inject the actual vaccine to be tested during certain pharmacokinetic and toxicology tests. For example, in study 2.6.5.5B, only 2 of the 4 lipid nanoparticle (LNP) components were labeled and injected into rats, and their distribution and persistence in many organs were assessed at animal necropsy, from 15 minutes to 48 hours post-injection. For most organs, at 48 hours the amount of the two LNP components in each organ was still increasing. Thus, the ultimate distribution and persistence of the LNPs are unknown. And we have no information regarding duration and persistence of the mRNA or spike protein production in organs based on this study.[14]

17. A surrogate for mRNA (coding for spike protein) was an entirely different mRNA (coding for luciferase) in LNP injected into mice. In study 2.6.5.5A, bioluminescence was measured in liver through 9 days as a surrogate measure, while no attempt was made to evaluate the presence of spike protein in animal tissues, including in the brains of the experimental animals.[15] These surprising omissions have significant potential safety implications.

18. Given that only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system, according to Lazarus et al., the high number of adverse events and deaths following COVID vaccines is alarming.[16] While the Pfizer vaccine has now been used for five months and administered to more than 60 million Americans, FDA has issued no new guidance about the vaccine based on these troubling data, apart from expanding its use in children.

19. The FDA must be aware that the only avenue for an injured party to claim benefits as a result of a COVID vaccine injury is the Countermeasures Injury Compensation Program (CICP).[17] The CICP requires petitioners to prove that the COVID vaccine caused their injuries; the program has an extremely short statute of limitations of one year. If the FDA, working with

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[14] Study 2.6.5.5.B Pharmacokinetics: Organ Distribution. SARS-CoV-2 mRNA Vaccine (English Portion) (BNT162, PF-07302048), pp. 15-18, https://www.pmda.go.jp/drugs/2021/P20210212001/.

[15] *Id.*

[16] *See* Lazarus et al., *Electronic Support for Public Health-Vaccine Adverse Event Reporting System*, AGENCY FOR HEALTHCARE RESEARCH AND QUALITY, DEPT. OF HEALTH AND HUMAN SERVICES (Sept. 30, 2010), https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system; Shimabukuro et al., *Safety monitoring in the Vaccine Adverse Event Reporting System* (*VAERS*), VACCINE (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/; S. Rosenthal and R. Chen, *The reporting sensitivities of two passive surveillance systems for vaccine adverse events*, AM J PUBLIC HEALTH (Dec. 1995), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1615747/.

[17] Health and Human Services Administration, *Countermeasures Injury Compensation Program* (*CICP*), https://www.hrsa.gov/cicp.

the vaccine manufacturers, does not compile and publish an accurate list of adverse reactions, which is required for licensing, then these petitioners will have virtually no opportunity to prove injury or receive compensation.

B. Effectiveness

20. As with safety data on COVID vaccines, effectiveness data continue to evolve. Recently CDC acknowledged "vaccine breakthrough cases" where vaccinated subjects fall ill and potentially transmit the virus. CDC acknowledges that a "small percentage of people who are fully vaccinated against COVID-19 will still get sick and some may be hospitalized or die from COVID-19. It's also possible that some fully vaccinated people might have infections, but not have symptoms (asymptomatic infections)."[18]

21. As of April 26, 2021, CDC reported over 9,000 "breakthrough cases" and 132 COVID-caused deaths among vaccinated people.[19] CDC tracks reports of breakthrough cases via the National Notifiable Diseases Surveillance System (NNDSS)[20] and has recently stopped reporting breakthrough cases absent death or hospitalization.[21] The British government has also identified efficacy problems stating, "The resurgence in both hospitalisations and deaths is dominated by those that have received two doses of the vaccine, comprising around 60% and 70% of the wave respectively."[22]

22. The U.K. data modelers attribute these rates to the high level of vaccine uptake in the most at-risk elderly age group.[23] Overall, the U.K. believes "evidence shows vaccines are ***sufficiently*** effective in reducing hospitalisations and deaths in those vaccinated."[24] The U.K. caveat "sufficiently" is significant compared to the unqualified "effective" label that the FDA currently permits to be communicated to the public.

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[18] CDC, *What You Should Know About the Possibility of COVID-19 Illness After Vaccination*; (updated April 21, 2021), https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html.

[19] CDC, *COVID-19 Breakthrough Case Investigations and Reporting* (updated April 30, 2021), https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[20] CDC, *National Notifiable Diseases Surveillance System* (*NNDSS*), https://wwwn.cdc.gov/nndss/.

[21] CDC, *COVID-19 Breakthrough Case Investigations and Reporting* (April 30, 2021), https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[22] *SPI-M-O: Summary of further modelling of easing restrictions – Roadmap Step 2*, p. 10 (Mar. 31, 2021), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/975909/S1182_SPI-M-O_Summary_of_modelling_of_easing_roadmap_step_2_restrictions.pdf.

[23] *Id*.

[24] GOV.UK; *COVID-19 Response-Spring 2021* (*Summary*) (Feb. 22, 2021), https://www.gov.uk/government/publications/covid-19-response-spring-2021/covid-19-response-spring-2021-summary.

C. Misbranding as "Safe, Effective and FDA Approved"

23. Recently the FDA sent a warning letter "RE: Unapproved and Misbranded Products Related to Coronavirus Disease 2019 (COVID-19)."[25] FDA warned that labeling COVID therapies as Safe, Effective or FDA Approved when they are not proven to be so by FDA standards violates § 505(a) of the FDCA, 21 U.S.C. § 355(a). The same standard should apply to COVID vaccines, as any such products are misbranded drugs and violate § 502 of the FDCA and 21 U.S.C. § 352.

24. The introduction or delivery for introduction of any such product into interstate commerce is prohibited under § 301(a) and (d) of the FDCA and 21 U.S.C. § 331(a) and (d). The FDA specifically warned a vendor: "We advise you to review your websites, product labels, and other labeling and promotional materials to ensure that you are not misleadingly representing your products as *safe and effective* for a COVID-19-related use for which they have *not been approved* by FDA and that you do not make claims that misbrand the products in violation of the FD&C Act."

25. FDA must ensure against misrepresenting COVID vaccine products as "safe and effective" when FDA has not so designated them. FDA's description of COVID vaccines pursuant to § 564(d)(3) of the Act states: "based on the totality of scientific evidence available to FDA…it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine *may be effective* in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act." The FDA language on effectiveness provides a qualification similar to the above-mentioned U.K. regulatory language. FDA's precise technical language to manufacturers does not match its unequivocal "effective" claims on official government websites, including that of the CDC, as illustrated below.[26]

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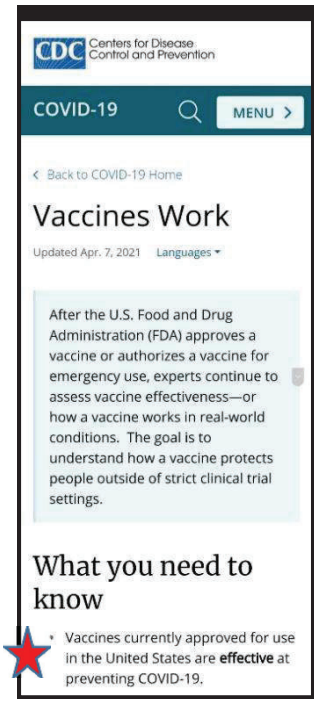
[25] FDA, *Warning Letter to Mercola.com, LLC* (Feb. 18, 2021), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mercolacom-llc-607133-02182021.

[26] CDC, *Key things to know about COVID-19 vaccines* (May 10, 2021), https://www.cdc.gov/coronavirus/2019-ncov/vaccines/keythingstoknow.html;

CDC, *Safety of COVID-19 vaccines* (udated May 11, 2021), https://www.cdc.gov/coronavirus/2019- ncov/vaccines/safety/safety-of-vaccines.html;

FDA, *Letter to Pfizer* (May 10, 2021), https://www.fda.gov/media/144412/download.



D. EUA revocation, additional EUAs, and off-label use clarification for COVID therapies

26. On February 4, 2020 the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves the virus that causes Coronavirus Disease (COVID-19). Based on this determination, the Secretary on March 27, 2020 declared that circumstances justify emergency use of drugs and biological products during the COVID-19 pandemic pursuant to § 564 of the FDCA (21 U.S.C. § 360bbb-3).

27. Since December 2020, several manufacturers have received EUAs for COVID vaccines. One of the criteria for these authorizations, beyond the existence of an emergency, is that there are "no adequate, approved, and available alternatives."[27] Many medical professionals and elected officials have objected to the inconsistent handling of EUAs for alternative treatments. Dr. Peter McCullough testified to the Texas Senate on March 10, 2021 that an 85% lower mortality rate from COVID would have been possible if government agencies had publicly recommended

[27] FDA, *Emergency Use Authorization* (updated May 11, 2021), https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization;

FDA, *FAQs on Emergency Use Authorizations (EUAs) for Medical Devices During the COVID-19 Pandemic* (updated April 23, 2021), https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/faqs-emergency-use-authorizations-euas-medical-devices-during-covid-19-pandemic.

early treatments.[28] Now that COVID cases and deaths are decreasing because many if not most Americans are immune, the relative benefit of COVID vaccines has diminished.[29]

28. Three U.S. Senators asked the FDA to clarify why it revoked the previously granted EUAs for hydroxychloroquine (HCQ) and chloroquine (CQ) and under what authority it regulates the practice of medicine. The Senators also asked what authority states have to regulate the prescribing and dispensing of drugs.[30] FDA issued and revoked EUAs for HCQ and CQ donated to the Strategic National Stockpile in a way that confused medical professionals, resulting in their reluctance to prescribe the drugs, including those not under EUA. FDA improperly recommended against the use of chloroquine drugs in outpatients, and against early treatment, which is when these antiviral drugs are likely to be effective. FDA appears to have collaborated with officials in dozens of states and even with certain pharmaceutical and pharmacy companies to restrict the prescribing and dispensing of chloroquine drugs against COVID. These unprecedented actions require explanation. The FDA must immediately revoke its recommendations for the limited use and withholding of these drugs during a life-threatening pandemic and must publicize its revocation widely.

29. Medical professionals also question FDA's approval of Investigational New Drug (IND) human trials performed by the University of Pittsburg (REMAP-COVID)[31] and the University of Philadelphia (PATCH)[32] using knowingly borderline lethal doses of HCQ in humans. There were more deaths in the HCQ arm than in the control arm of the REMAP-COVID study and in the other two large multicenter studies, the Solidarity and Recovery studies, that used excessive doses. The PATCH study ended after enrolling only 5 subjects.

30. In other FDA guidance regarding the chloroquine drugs, FDA made the misleading claim that "Hospitalized patients were likely to have greater prospect of benefit (compared to

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[28] Dr. Peter McCullough's testimony to the Texas Senate HHS Committee (Mar. 10, 2021), https://www.youtube.com/watch?v=QAHi3lX3oGM.

[29] Dr. Peter McCullough et al., *SARS-CoV-2 mass vaccination: Urgent questions on vaccine safety 2 that demand answers from international health agencies, regulatory 3 authorities, governments and vaccine developers* (May 8, 2021), https://www.andrewbostom.org/wp-content/uploads/2021/05/Bruno-et-al.-Vaccine-Safety-Urgent-Manuscript-Preprint-May-8-2021.pdf.

[30] Senators Ted Cruz, Mike Lee, Ron Johnson, *Letter to FDA Commissioner Stephen Hahn* (Aug. 18, 2020), https://www.hsgac.senate.gov/imo/media/doc/2020-08-18%20RHJ%20Letter%20to%20FDA%20on%20HCQ%20+%20CQ.pdf.

[31] UNIVERSITY OF PITTSBURG, Department of Critical Care, *UPMC Leads Global Efforts to Fast-track COVID-19 Therapies*, https://www.ccm.pitt.edu/node/1110.

[32] *Penn Launches Trial to Evaluate Hydroxychloroquine to Treat, Prevent COVID-19*, PENN MEDICINE NEWS (April 3, 2020), https://www.pennmedicine.org/news/news-releases/2020/april/penn-launches-trial-to-evaluate-hydroxychloroquine-to-treat-prevent-covid19;

The PATCH Trial (*Prevention And Treatment of COVID-19 With Hydroxychloroquine*) (*PATCH*), CLINICALTRIALS.GOV (updated Dec. 10, 2020), https://clinicaltrials.gov/ct2/show/NCT04329923.

ambulatory patients with mild illness)," and that chloroquine drugs have a "slow onset of action." In its justification for restricting the use of chloroquine drugs, FDA also opined that "it is no longer reasonable to believe that oral formulations of HCQ and CQ may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks."[33]

31. These claims fly in the face of substantial evidence of positive effects of the drugs when used early in the disease at usual, approved, therapeutic doses. FDA has chosen to ignore the many trials that were properly conducted. The FDA buttresses its contention of the dangers of these drugs based in part on the FDA-approved trial and other trials that administered excessive, non-therapeutic doses of HCQ and resulted in more deaths in the treated group than the placebo group.

32. Similarly, FDA exhibited bias regarding the effective and safe use of ivermectin for prophylactic use of COVID. In March 2021, the agency stated: "The FDA has not reviewed data to support use of ivermectin in COVID-19 patients to treat or to prevent COVID-19; however, some initial research is underway."[34] Yet already on April 10, 2020, FDA had issued a public warning against the use of ivermectin because, it claimed, Americans were purchasing over the counter (OTC) veterinary ivermectin as a COVID treatment.[35] Research from Australia had been published online a week earlier, on April 3, 2020, supporting use of ivermectin for COVID based on in vitro studies.[36]

33. Thus, FDA was aware at least 13 months ago that Americans were using ivermectin to treat and prevent COVID. How could FDA not have reviewed data on ivermectin during an entire year after it was informed about this use? That was a year during which dozens of studies about the drug's use were available as publications or preprints for both prophylaxis and treatment; during which there was a Senate hearing on the drug; and during which half a million Americans died from the disease, who had not been treated with effective medications because of FDA guidance.

34. Furthermore, ivermectin has been used OTC for COVID in many countries and regions with excellent reported treatment success. The drug's safety has been established with at

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[33] FDA Letter revoking EUA for Hydroxychloroquine (Jun. 15, 2020), https://www.fda.gov/media/138945/download.

[34] FDA, *Why You Should Not Use Ivermectin to Treat or Prevent COVID-19* (updated May 10, 2021), https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19.

[35] FDA Letter to Stakeholders, *Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans* (April 10 2020), https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans.

[36] Leon Caly, Julian D. Druce, *The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro*, ANTIVIRAL RESEARCH, vol. 178, 104787 (Jun. 2020), https://reader.elsevier.com/reader/sd/pii/S0166354220302011.

least a billion doses used, and the drug is on the World Health Organization's list of essential drugs.

35. Many medical professionals suspect FDA's feigned ignorance about the drug was a prerequisite to issuing EUAs for COVID vaccines, given the EUA requirement that no approved drug may be available for the same indication. Ivermectin and hydroxychloroquine, both of which have extremely long biological half lives, can be given infrequently as prophylaxis for COVID. Hydroxychloroquine or chloroquine are used weekly to prevent malaria, and they have been used in the same way to prevent COVID. Ivermectin can be used once or twice yearly to prevent river blindness (onchocerciasis), and it has been used weekly or bi-weekly to prevent COVID. Many clinical trials have documented the benefits of both drugs for COVID prevention. Yet FDA has remained silent about these benefits, even though the efficacy of these preventive treatments probably supercedes that of COVID vaccines.

36. This petition encourages FDA to expeditiously evaluate existing ivermectin research and issue accurate guidance for its use against COVID, e.g., where "18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance."[37] Additional studies have found it highly effective for both pre- and post-exposure prophylaxis of COVID.[38]

37. Finally, reflecting on the FDA's regulatory history is helpful: A proven association between the 1976–1977 swine influenza vaccine and approximately 400 cases of Guillain–Barré syndrome halted that particular national vaccination campaign.[39] The reported deaths following

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[37] P. Kory, G. Meduri et al., *Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19*, AMERICAN JOURNAL OF THERAPEUTICS (May-Jun 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8088823/.

Ahmed, Sabeena et al., *A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness*, INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES, vol. 103, pp. 214-216 (Feb. 2021), https://pubmed.ncbi.nlm.nih.gov/33278625/;

Jans D. A. and Wagstaff K. M., *The broad spectrum host-directed agent ivermectin as an antiviral for SARS-CoV-2*? BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 538, pp. 163-172 (2021), https://pubmed.ncbi.nlm.nih.gov/33341233/.

Formiga, Fabio Rocha et al., *Ivermectin: an award-winning drug with expected antiviral activity against COVID-19*, JOURNAL OF CONTROLLED RELEASE, vol. 329, pp. 758-761 (Jan. 2021), https://pubmed.ncbi.nlm.nih.gov/33038449/.

Bhowmick, Subhrojyoti et al., *Safety and Efficacy of Ivermectin and Doxycycline Monotherapy and in Combination in the Treatment of COVID-19: A Scoping Review*, DRUG SAFETY, pp. 1-10 (Apr. 16, 2021), https://pubmed.ncbi.nlm.nih.gov/33864232/.

[38] *Ivermectin for COVID-19: real-time meta analysis of 55 studies*, COVID ANALYSIS (version 81, May 15, 2021), https://ivmmeta.com/.

[39] *See* CDC, H1N1 Flu, FACT SHEET: GUILLAIN- BARRÉ SYNDROME (GBS) (Dec. 15, 2009), https://www.cdc.gov/h1n1flu/vaccination/factsheet_gbs.htm#:~:text=Getting%20GBS%20from%20a%20vaccination,got%20the%20swine%20flu%20vaccine.

that swine flu vaccination campaign, 30 out of 40-45 million vaccinees,[40] were insignificant compared to the current reported death toll of 4,434 due to COVID vaccines, Today's death rate is more than 50 times higher than that which ended the swine flu vaccine campaign.

38. Regarding the halted swine flu vaccine program, the CDC's *Emerging Infectious Diseases Journal* concluded, "In 1976, the federal government wisely opted to put protection of the public first."[41] FDA should learn from this past experience and again put protection of the public first. It is imperative that the FDA swiftly take action to authorize alternative treatments.

E. Children

39. According to the National Center for Health Statistics data as of May 5, 2021, 282 children have died "involving COVID," whereas over 560,000 Americans have died "involving COVID."[42] Three thousand children have been diagnosed with a multi-system inflammatory disorder, of whom about 1%, or approximately 30, have died. Thus the relative risk for children due to COVID is very low.

40. By contrast, recent VAERS reports include the deaths of several children following COVID vaccination.[43] Five of the child death reports footnoted below involve apparent cardiac related deaths, and two were infants. There is one reported death in a 15 year old after receiving the Pfizer BioNTech vaccine, and another reported death of a 15 year old after receiving a Moderna

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[40] Rick Perlstein, *Gerald Ford Rushed Out a Vaccine. It Was a Fiasco*, THE NEW YORK TIMES (Sept. 2, 2020), https://www.nytimes.com/2020/09/02/opinion/coronavirus-vaccine-trump.html; Donald G. McNeil, Jr., *Don't Blame Flu Shots for All Ills, Officials Say*, THE NEW YORK TIMES (Sept 27, 2009), https://www.nytimes.com/2009/09/28/health/policy/28vaccine.html.

[41] Sencer D. J., Millar J., *Reflections on the 1976 Swine Flu Vaccination Program*, EMERGING INFECTIOUS DISEASES, Vol. 12, No. 1, pp. 29-33 (Jan. 2006), https://wwwnc.cdc.gov/eid/article/12/1/05-1007_article.

[42] CDC, *Weekly Updates by Select Demographic and Geographic Characteristics*, Provisional Death Counts for Coronavirus Disease 2019 (COVID-19) (updated May 12, 2021), https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge.

[43] VAERS reports include:

A 1-year-old, https://medalerts.org/vaersdb/findfield.php?IDNUMBER=1261766&WAYBACKHISTORY=ON;

a 2-year-old, https://medalerts.org/vaersdb/findfield.php?IDNUMBER=1255745&WAYBACKHISTORY=ON;

two 15-year-olds, https://www.medalerts.org/vaersdb/findfield.php?IDNUMBER=1187918 and https://www.medalerts.org/vaersdb/findfield.php?IDNUMBER=1242573;

two 16-year-olds, https://www.medalerts.org/vaersdb/findfield.php?IDNUMBER=1225942;

a 17-year old, https://www.openvaers.com/openvaers/1199455;

and an infant, https://www.medalerts.org/vaersdb/findfield.php?IDNUMBER=1166062.

vaccine. Each child must have been enrolled in a clinical trial, since their ages would have precluded them getting the vaccine legally under the EUA. There were only about 1,000 children in the 12-15 year age group in the vaccine arm of Pfizer's trial and probably about the same number in the vaccine arm of Moderna's trial. Thus, the death rate following either vaccination in this age group, assuming these children were trial enrollees, is approximately 2 in 2,000 or 0.1%.

41. There are 74 million children in the United States. So far, 282 have died "involving Covid." Two hundred eighty-two in 74 million is a rate of 0.00038%. While many children may not have been exposed to COVID, CDC estimated that 22.2 million children aged 5-17 had had COVID and 127 had died, at the May 12, 2021 meeting of the Advisory Committee on Immunization Practices, or 0.00057%.[44] Available evidence strongly suggests that the vaccine is much more dangerous to children than the disease.

42. A recent opinion piece in the *British Medical Journal* noted that "the likelihood of severe outcomes or death associated with COVID-19 infection is very low for children, undermining the appropriateness of an emergency use authorization for child covid-19 vaccines."[45] The authors also suggested child vaccinations could strategically harm vaccination efforts and increase vaccine hesitancy.[46]

F. Servicemembers' Prior Consent

43. Certain citizens and elected officials have recently encouraged the President of the United States to waive U.S. Servicemembers' right to prior consent for COVID vaccines.[47] According to 10 U.S.C. §1107(f), only the President of the United States may order such a waiver if he determines, in writing, that obtaining consent is not in the national security interest. The intent of any waiver of consent must be related to a member's participation in a "particular military operation," as opposed to the broad sweep some are encouraging.

44. Such a waiver is only permissible when obtaining prior consent is infeasible or contrary to the best interests of the military member. Clearly, prior consent for current servicemembers is feasible for COVID vaccines.[48] Because the President's authority is contingent on the standards set forth in § 505(i)(4) of the FDCA and 21 U.S.C. § 355(i)(4), and since the chain of command requires consultation with HHS, the FDA may issue guidance to the President on this

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[44] Helen Branswell, *CDC advisory group gives green light to Pfizer's Covid vaccine for adolscents*," STAT (May 12, 2021), https://www.statnews.com/2021/05/12/cdc-advisory-group-gives-green-light-to-pfizers-covid-vaccine-for-adolescents/.

[45] W. Pegden, V. Prasad, S. Baral, *Covid vaccines for children should not get emergency use authorization*, BMJ (May 7, 2021), https://blogs.bmj.com/bmj/2021/05/07/covid-vaccines-for-children-should-not-get-emergency-use-authorization/.

[46] *Id.*

[47] Jimmy Panetta, *Letter to President Biden* (Mar. 24, 2021), https://www.documentcloud.org/documents/20521870-panetta_dod-covid-vaccine-waiver.

[48] 21 U.S.C. § 50.23: Exception from general requirements, https://www.ecfr.gov/cgi-bin/text-idx?node=se21.1.50_123&rgn=div8.

matter.[49]

45. The specific law on EUA vaccines was codified in 10 U.S.C. § 1107a.[50] The § 1107a language is similar to § 1107(f) to ensure that troops are granted prior consent and have the "option to accept or refuse administration of a product." National leaders should continue to honor and respect servicemembers' rights. No President has ever waived servicemembers' prior consent under 10 U.S.C. § 1107(f) or 10 U.S.C. § 1107a, and FDA should advise that current circumstances do not warrant such drastic action.

G. Coercion and Compulsion

46. COVID vaccines are optional in accordance with 21 C.F.R. § 360bbb-3(e)(1)(a) as EUA products.[51] Yet throughout the United States, schools, businesses, government and industry are using coercive tactics to encourage, incentivize and compel COVID vaccination as a condition of employment, education and daily living. It is unlikely that most Americans would support such coercion if they were fully informed that COVID vaccines are for emergency use only, investigational, unapproved, and that individuals have the explicit right to refuse by law. Some states are considering or have approved legislation or executive action to bar vaccine mandates.[52] Some professional medical associations also have expressed opposition to these coercive tactics.[53]

47. Coercion and compulsory vaccination are inconsistent with the legal requirements to inform both healthcare workers administering EUA vaccines and vaccine recipients of the significant known and unknown benefits and risks of such use. Most importantly, the FDA must ensure all parties are aware of the "option to accept or refuse" administration of all EUA products and that alternatives are available. These disclosure requirements are entirely inconsistent with coercion, and government agencies should not publish information that violates the law. Information on the government websites of the Equal Employment Opportunity Commission

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[49] *Id.*

[50] 10 U.S.C. § 1107a - Emergency use products, https://www.govinfo.gov/app/details/USCODE-2010-title10/USCODE-2010-title10-subtitleA-partII-chap55-sec1107a/summary.

[51] § 360bbb–3. Authorization for medical products for use in emergencies, https://www.govinfo.gov/content/pkg/USCODE-2011-title21/pdf/USCODE-2011-title21-chap9-subchapV-partE-sec360bbb-3.pdf.

[52] Pearson L., Brofsky J., et al., *50-state Update on Pending Legislation Pertaining to Employer-mandated Vaccination*, HUSCH BLACKWELL (updated April 20, 2021), https://www.huschblackwell.com/newsandinsights/50-state-update-on-pending-legislation-pertaining-to-employer-mandated-vaccinations.

[53] Dr. Paul M. Kempen, *Open Letter from Physicians to Universities: Allow Students Back Without COVID Vaccine Mandate*, ASSOCIATION OF AMERICAN PHYSICIANS AND SURGEONS (Apr. 24, 2021), https://aapsonline.org/open-letter-from-physicians-to-universities-reverse-covid-vaccine-mandates/.

(EEOC)[54] and the Occupational Safety and Health Administration (OSHA)[55] in fact ignore these federal disclosure requirements.

48. The armed forces' experience with the very first EUA vaccine mandate against anthrax is instructive.[56] The military now administers the anthrax vaccine on a voluntary basis with informed consent, but only after a federal court halted the mandatory anthrax vaccine program because the FDA had improperly issued a license.[57]

49. The only language in the EUA law, 21 U.S.C. § 360bbb-3(e)(1)(A)(ii)(I-III), that could possibly be construed to imply mandates is the term "consequences" in clause III. Both statutory analysis and legislative history suggest that it is far more likely that this term applies to health-related consequences only, i.e., medical risks and benefits, since that is the topic of that statute section and because it does not refer to punitive measures or consequences, such as termination of employment or education.[58]

50. Another hazard of coercive policies and broad liability for industry is reliance on subpar manufacturers. One of the COVID vaccine manufacturing subcontractors today, Emergent BioSolutions, is the same company, with the same President and Board Chairman, which the FDA cited under its previous name, BioPort, for numerous violations of Good Manufacturing Practices.[59] The image below, taken from an FDA form in 2000, shows the citation to BioPort for

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[54] EEOC, *What You Should Know About COVID-19 and the ADA, the Rehabilitation Act, and Other EEOC Laws*, §§ K1 & K7 (updated Dec. 16, 2020), https://www.eeoc.gov/wysk/what-you-should-know-about-covid-19-and-ada-rehabilitation-act-and-other-eeo-laws.

[55] Jeff Yoders, *OSHA Imposes New Guidance For Employer-Required COVID-19 Vaccines*, ENR (May 3, 2021), https://www.enr.com/articles/51691-osha-imposes-new-guidance-for-employer-required-covid-19-vaccines.

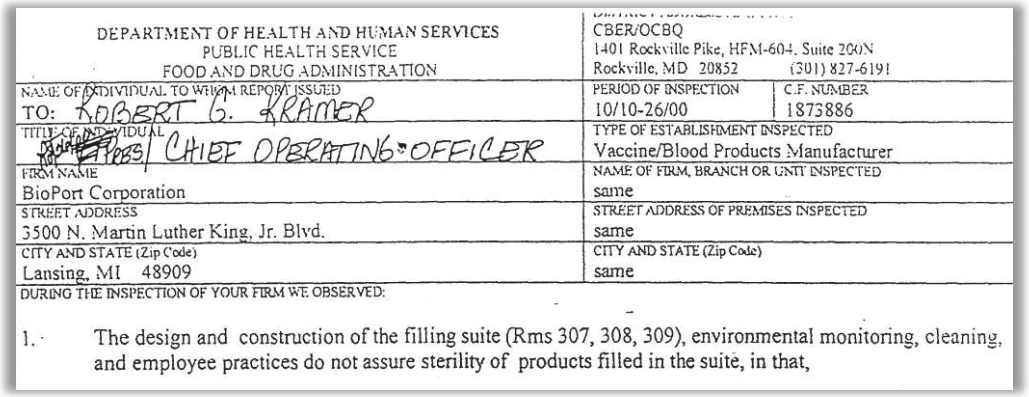
[56] FDA, *Anthrax Vaccine Adsorbed (AVA) EUA –ARCHIVED INFORMATION*, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information#anthrax.

[57] *Determination and Declaration Regarding Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax*, FEDERAL REGISTER (Feb. 2, 2005), https://www.federalregister.gov/documents/2005/02/02/05-2027/determination-and-declaration-regarding-emergency-use-of-anthrax- vaccine-adsorbed-for-prevention-of?fbclid=IwAR22J58y3SQ2tVoEUlNgZVU-PmRxoou0P05i9WqS4SUiOcj9HyaiUJ8Dvrg.

[58] Parasidis E., Kesselheim A. S., *Assessing The Legality Of Mandates For Vaccines Authorized Via An Emergency Use Authorization*, HEALTH AFFAIRS (Feb. 16, 2021), https://www.healthaffairs.org/do/10.1377/hblog20210212.410237/full/.

[59] Richard Luscombe, *Emergent chief sold $10m in stock before company ruined 15m Covid vaccines*, THE GUARDIAN (Apr. 26, 2021), https://www.theguardian.com/business/2021/apr/26/emergent-biosolutions-robert-kramer-stock-covid-vaccines-error.

deviations from acceptable manufacturing standards for vaccines.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CBER/OCBQ
1401 Rockville Pike, HFM-604, Suite 200N
Rockville, MD 20852 (301) 827-6191

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: ROBERT G. KRAMER

PERIOD OF INSPECTION: 10/10-26/00
C.F. NUMBER: 1873886

TITLE OF INDIVIDUAL
CHIEF OPERATING OFFICER

TYPE OF ESTABLISHMENT INSPECTED
Vaccine/Blood Products Manufacturer

FIRM NAME
BioPort Corporation

NAME OF FIRM, BRANCH OR UNIT INSPECTED
same

STREET ADDRESS
3500 N. Martin Luther King, Jr. Blvd.

STREET ADDRESS OF PREMISES INSPECTED
same

CITY AND STATE (Zip Code)
Lansing, MI 48909

CITY AND STATE (Zip Code)
same

DURING THE INSPECTION OF YOUR FIRM WE OBSERVED:

1. The design and construction of the filling suite (Rms 307, 308, 309), environmental monitoring, cleaning, and employee practices do not assure sterility of products filled in the suite, in that,

51. Today, Emergent BioSolutions, despite apparent FDA oversight, shipped out unauthorized bulk COVID vaccine ingredients for finishing and filling. Emergent BioSolutions shipped those ingredients to another entity, and the shipments eventually reached buyers in at least four other countries, according to the *New York Times*.[60] The FDA halted distribution in the U.S. and cited quality deviations[61] that mirrored those that American servicemembers witnessed 20 years ago with the anthrax vaccine.[62] People need to be informed about these manufacturing deviation patterns given the importance and wide use of these products.

52. States may lawfully mandate certain vaccines. But that is not the case for investigational, unapproved EUA medical products. The preemption doctrine,[63] based on the Supremacy Clause of the U.S. Constitution, Article VI., § 2,[64] requires that the federal requirements for informed consent supersede state laws and regulations that may violate EUA provisions. The FDA should support, defend and enforce federal laws that govern biologics,

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[60] Chris Hamby, *Baltimore Vaccine Plant's Troubles Ripple Across 3 Continents*, THE NEW YORK TIMES (May 6, 2021), https://www.nytimes.com/2021/05/06/world/baltimore-vaccine-countries.html.

[61] FDA, HHS, Form FDA 483, Inspectional Observations (Apr. 20, 2021), https://www.fda.gov/media/147762/download.

[62] Historic FDA Form 483 Deviation Report Documenting that "The manufacturing process for Anthrax Vaccine is not validated." https://nebula.wsimg.com/30662205620a26a4b21274dc49888891?AccessKeyId=0BA19F97E21CB8613CD7&disposition=0&alloworigin=1.

[63] *Preemption*, CORNELL LAW SCHOOL, Legal Information Institute, https://www.law.cornell.edu/wex/preemption.

[64] U.S. Const. art. VI., § 2 , "This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." https://www.archives.gov/founding-docs/constitution-transcript.

including EUA products. The option to refuse COVID vaccines is codified in federal law, and President Biden has affirmed this, saying, "I don't think it [vaccination against COVID] should be mandatory. I wouldn't demand it to be mandatory."[65]

H. Conclusion to Statement of Grounds

53. The FDA's mission is "protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products."[66] President Roosevelt's signing of the Federal Food, Drug, and Cosmetic Act (FDCA) closed many safety and efficacy loopholes and improved the landscape of consumer protection forever.[67] The 1962 Harris-Kefauver amendment[68] set in motion regulatory standards for biologics licensure that require proven efficacy, and the 1972 review sought to ensure proof of efficacy and no misbranding for biologics. These historic advances require reflection. The preamble to the 1972 review stated, '"The importance to the American public of safe and effective vaccines…and other biological products cannot be overstated."[69]

54. Biologics, as with all drugs and devices, must have adequate directions for use and be proven safe and effective before FDA approval and licensure. The FDA erred with the anthrax vaccine, and it took a Citizen Petition[70] and federal court decision to make the FDA comply with the FDCA.[71] At other times, the FDA has upheld its mission without prompting to make tough regulatory rulings, as the Supreme Court has acknowledged.[72] With this Petition, we look forward

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[65] Julia Manchester, *Biden: Coronavirus vaccine should not be mandatory*, THE HILL (Apr. 12, 2021), https://thehill.com/homenews/campaign/528834-biden-coronavirus-vaccine-should-not-be-mandatory.

[66] FDA, *What We Do*; https://www.fda.gov/about-fda/what-we-do#mission.

[67] FDA, *80 Years of the Federal Food, Drug, and Cosmetic Act* (Nov. 7, 2018), https://www.fda.gov/about-fda/fda-history-exhibits/80-years-federal-food-drug-and-cosmetic-act.

[68] FDA, *Kefauver-Harris Amendments Revolutionized Drug Development* (Oct. 9, 2012), https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development.

[69] HHS, FDA, *Biological Products March 1936-March 1978*, Preamble, p. 56, 37 Fed. Reg. 16679.

[70] Citizen Petition, FDA Docket 01P-0471/CP1, https://img1.wsimg.com/blobby/go/4fa7f468-a250-4088-926e-3c56a998df1f/downloads/citizen%20petition%20ava%20rempfer%20dingle.pdf?ver=1620969217312, and Response thereto, https://downloads.regulations.gov/FDA-2001-P-0119-0003/attachment_1.pdf.

[71] *Doe # 1 v. Rumsfeld*, 297 F. Supp. 2d 119, 135; see par. F, reference to Citizen Petition, FDA docket 01p-0471, https://nebula.wsimg.com/2617051f041708e6b5335b6c885478d7?AccessKeyId=0BA19F97E21CB8613CD7&disposition=0&alloworigin=1.

[72] U.S. Reports: *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609 (1972), https://tile.loc.gov/storage- services/service/ll/usrep/usrep412/usrep412609/usrep412609.pdf.

to the FDA's appropriate, tough regulatory action to bring its COVID vaccine regulations and guidance into line with federal law.

55. Although EUA law is relatively recent, we ask the FDA to be ever cognizant of its longstanding, statutory mission and duty to protect the public health and to ensure that the American public receives only safe and effective vaccines. Most Americans are not aware of the strict compliance requirements for EUA COVID vaccines nor do they know that these biologics are "investigational" and "unapproved medical products."[73] They do not know that the FDA has not fully approved these vaccines as safe and effective under the FDCA. The reason Americans are unaware is because the FDA has failed to provide and enforce accurate public messaging. Reversing this trend is imperative; the FDA must comply with law.

56. Acting on this Citizen Petition will enhance the FDA's credibility with the public. Given the obvious safety, effectiveness, labeling and branding concerns over COVID vaccines detailed above, along with anticipated comments on this docket, we respectfully appeal to the FDA to implement the actions requested in this Petition.

III. ENVIRONMENTAL IMPACT

57. The undersigned hereby state that the relief requested in this Petition will have no environmental impact, and therefore an environmental assessment is not required under 21 C.F.R. §§ 25.30 and 25.31.

IV. ECONOMIC IMPACT

58. Economic impact information will be submitted upon request of the Acting Commissioner.

V. CERTIFICATION

59. The undersigned certify that, to their best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioners that are unfavorable to the Petition.

Respectfully submitted,

/s/ Meryl Nass
Meryl Nass, MD, Scientific Advisory Board Member

/s/ Robert F. Kennedy, Jr.
Robert F. Kennedy, Jr., Board Chair and Chief Litigation Counsel

[73] FDA, *Emergency Use Authorization for Vaccines explained* (updated Nov. 20, 2020), https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained.

Exhibit 3

August 23, 2021

Meryl Nass, M.D.
Robert F. Kennedy, Jr.
Children's Health Defense
1227 North Peachtree Parkway
Suite 202
Peachtree City, GA 30269

Re: Citizen Petition (Docket Number FDA-2021-P-0460)

Dear Dr. Nass and Mr. Kennedy,

This letter responds to the citizen petition dated May 16, 2021 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Children's Health Defense (Petitioner) relating to: clinical trials, Emergency Use Authorization, licensure, and advertising and promotion of vaccines to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the Petition).

In the Petition, Petitioner requests that FDA:

1. "revoke all EUAs and refrain from approving any future EUA, NDA, or BLA for any COVID vaccine for all demographic groups";
2. "immediately refrain from allowing minors to participate in COVID vaccine trials, refrain from amending EUAs to include children, and immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines";
3. "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect";
4. "immediately amend [FDA's] existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID…and immediately issue notifications to all stakeholders";
5. "issue guidance to the Secretary of the Defense [sic] and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers [sic]";
6. "issue guidance…to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences"; and

7. "[p]ending revocation of COVID vaccine EUAs, FDA should issue guidance that all marketing and promotion of COVID vaccines must refrain from labeling them 'safe and effective.'"

Petition at 1-2.

In this letter, we discuss the safety of licensed and authorized vaccines. We then turn to the requests contained in the Petition. We consider each of your requests in light of the legal standards for FDA action, and provide our conclusions based on the facts, the science, and the law.

This letter responds to the Petition in full. FDA has carefully reviewed the Petition and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR § 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

Here is an outline of our response:

I. Background
II. Vaccines That Are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements
    a. Vaccines that are FDA-Licensed are Safe
        i. Vaccines that are FDA-Licensed are Shown to Be Safe at the Time of Licensure
        ii. Vaccine Safety Continues to Be Monitored Post-Licensure
    b. An Emergency Use Authorization for a COVID-19 Preventative Vaccine Is Issued Only If the Relevant Statutory Standards Are Met
III. Discussion
    a. Investigational New Drugs
    b. The Citizen Petition
        i. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines and Refrain from Issuing any Future EUA or Approving any Future NDA, or BLA for any COVID-19 Vaccine for all Demographic Groups because the Current Risks of Serious Adverse Events or Deaths Outweigh the Benefits, and Because Existing, Approved Drugs Provide Highly Effective Prophylaxis and Treatment against COVID-19, Mooting the EUAs
            1. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines
            2. Petitioner's Request to Refrain from Granting any Future EUA for a COVID-19 Vaccine for any Population
            3. Petitioner's Request to Refrain from Approving any Future NDA for any COVID-19 Vaccine for any Population

I. Background

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration

of a public health emergency related to COVID-19.[1]On February 4, 2020, pursuant to section 564 of the FD&C Act (21 U.S.C. § 360bbb-3), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[2] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act.[3] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[4]

Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been completed. Between December 11, 2020 and February 27, 2021, FDA issued emergency use authorizations for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer); ModernaTX, Inc. (Moderna); and Janssen Biotech, Inc. (Janssen), a pharmaceutical company of Johnson & Johnson. FDA received a Biologics License Application (BLA) for the COVID-19 vaccine, BNT162b2, intended to prevent COVID-19 in individuals 16 years of age and older. As announced by FDA on August 23, 2021, the Agency is issuing a biologics license for this COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) to BioNTech Manufacturing GmbH.[5]

II. Vaccines That Are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements

a. Vaccines that are FDA-Licensed are Safe

i. Vaccines that are FDA-Licensed Are Shown to Be Safe at the Time of Licensure

FDA has a stringent regulatory process for licensing vaccines.[6,7] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have

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[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Originally issued on Jan. 31, 2020, and subsequently renewed), https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

[2] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

[3] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ .

[5] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH (hereinafter "BioNTech"). The basis for FDA's licensure decision is set forth in FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech application. This memorandum will be posted on fda.gov. We incorporate by reference the SBRA for the BLA.

[6] CDC, Ensuring the Safety of Vaccines in the United States, February 2013, https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-ensuring-bw-office.pdf.

[7] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

been demonstrated to be "safe, pure, and potent."[8] Prior to approval by FDA, vaccines are extensively tested in non-clinical studies and in humans. FDA's regulations describe some of the extensive data and information that each sponsor of a vaccine must submit to FDA in order to demonstrate the product's safety before FDA will consider licensing the vaccine. FDA requires that the sponsor's biologics license application (BLA) include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and a representative sample of the product and summaries of results of tests performed on the lot(s) represented by the sample.[9]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its approved indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a vaccine has been demonstrated.[10] Only when FDA's standards are met is a vaccine licensed.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[11] Therefore, the manufacturers of vaccines that have been licensed in the U.S. have necessarily demonstrated the safety of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

For more information on FDA's thorough process for evaluating the safety of vaccines, see Appendix I of this letter, *Aspects of Vaccine Development and Process for Licensure*.

ii. Vaccine Safety Continues to Be Monitored Post-Licensure

FDA's oversight of vaccine safety continues after licensure of the product. Once the licensed vaccine is on the market, post-marketing surveillance of vaccine safety is conducted in order to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. FDA employs multiple surveillance systems and databases to continue to evaluate the safety of these vaccines. In certain cases, FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.

b. An Emergency Use Authorization for a COVID-19 Preventative Vaccine Is Issued Only If the Relevant Statutory Standards Are Met

Congress established the Emergency Use Authorization (EUA) pathway to ensure that, during public health emergencies, potentially lifesaving medical products could be made available before being approved. The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of

[8] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[9] 21 CFR § 601.2(a).
[10] FDA, Vaccines, last updated January 2021, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[11] 21 CFR § 601.2(d) (emphasis added).

threats. When such a declaration is made, FDA may issue an EUA, which is different from the regulatory process for vaccine licensure.

Section 564 of the Food Drug & Cosmetic Act (FD&C Act) (21 U.S.C. § 360bbb-3) authorizes FDA to, under certain circumstances, issue an EUA to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, or nuclear threat agents when there are no adequate, approved, and available alternatives.

On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.[12] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[13]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the following statutory requirements are met:

- The agent referred to in the March 27, 2020 EUA declaration by the Secretary (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Although EUAs are governed under a different statutory framework than BLAs, FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document *Emergency Use Authorization for Vaccines to Prevent COVID-19* (October 2020 Guidance), FDA has provided recommendations that describe key information

[12] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[13] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

that would support issuance of an EUA for a vaccine to prevent COVID-19.[14] In the October 2020 Guidance, FDA explained that, in the case of such investigational vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[15] FDA has also stated, in this guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[16]

A Phase 3 trial of a vaccine is generally a large clinical trial in which a large number of people are assigned to receive the investigational vaccine or a control. In general, in Phase 3 trials that are designed to show whether a vaccine is effective, neither people receiving the vaccine nor those assessing the outcome know who received the vaccine or the comparator.

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome be reliable enough so that it is not likely to have happened by chance.[17] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Investigational COVID-19 vaccines continue to be studied in Phase 2 or Phase 3 trials. Following clinical trials, manufacturers analyze data prior to submitting to FDA a BLA to request approval from FDA to market the vaccine. A BLA for a new vaccine includes information and data regarding the safety, effectiveness, chemistry, manufacturing and controls, and other details regarding the product. During the current public health emergency, manufacturers may, with the requisite data and taking into consideration input from FDA, choose to submit a request for an EUA.

Importantly, FDA has made clear that any vaccine that meets FDA's standards for effectiveness is also expected to meet the Agency's safety standards. FDA has stated that the duration of safety follow-up for a vaccine authorized under an EUA may be shorter than with a BLA (which the Agency expects will ultimately be submitted by manufacturers of vaccines that are authorized under an EUA). Specifically, FDA's guidance to manufacturers recommends that data from Phase 3 studies to support an EUA include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[18] Furthermore, robust safety monitoring is conducted after a vaccine is made available. The monitoring systems include the

[14] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020 (October 2020 Guidance), https://www.fda.gov/media/142749/download.
[15] Id. at 3.
[16] Id. at 4.
[17] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.
[18] October 2020 Guidance at 10-11.

Vaccine Adverse Event Reporting System (VAERS), FDA's Biologics Effectiveness and Safety (BEST) System, and the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink. In addition, FDA has a partnership with the Centers for Medicare & Medicaid Services (CMS) to study vaccine safety. Other tools to monitor vaccine safety are under development. Collectively, these programs will help detect any new, unusual and rare side effects after vaccination that might not have been observed during clinical trials, as well as monitor for increases in any known side effects.

It is FDA's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to evaluate the vaccine and would also work towards submission of a BLA as soon as possible.

III. Discussion

The Petition makes a request regarding clinical trials of COVID-19 vaccines that include or propose to include children. FDA's investigational new drug process applies to the development of new drugs and biological products, including vaccines.[19]

a. Investigational New Drugs

Before a vaccine is licensed (approved) by FDA for use by the public, FDA requires that it undergo a rigorous and extensive development program to determine the vaccine's safety and effectiveness. This development program encompasses preclinical research (laboratory research, animal studies[20]) and clinical studies. At the preclinical stage, the sponsor focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Clinical studies, in humans, are conducted under well-defined conditions and with careful safety monitoring through all the phases of the investigational new drug process. FDA's regulations governing the conduct of clinical investigations are set out at 21 CFR Part 312.

Before conducting a clinical investigation in the U.S. in which a new drug or biological product is administered to humans, a sponsor must submit an investigational new drug application (IND) to FDA.[21] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[22] In addition to other information, an IND must contain information on clinical protocols and clinical investigators. Detailed protocols for proposed clinical studies permit FDA to assess whether the initial-phase trials will expose subjects to unnecessary risks. Information on the qualifications of clinical investigators (professionals, generally physicians, who oversee the administration of the experimental drug) permits FDA to assess whether they are qualified to fulfill their clinical trial duties. The IND

[19] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).
[20] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.
[21] See 21 CFR § 312.20(a).
[22] For additional information regarding the IND review process and general responsibilities of sponsor-investigators related to clinical investigations see Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators; Draft Guidance for Industry, May 2015, https://www.fda.gov/media/92604/download.

includes commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB),[23] and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[24]

FDA's regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, the initial human studies, referred to as Phase 1 studies, are generally safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects such as redness and swelling at the injection site or fever and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

Additionally, FDA regulations require that an IRB must review clinical investigations involving children as subjects covered by 21 CFR 50, subpart D and only approve those clinical investigations involving children as subjects that satisfy the criteria in 21 CFR 50, subpart D, Additional Safeguards for Children in Clinical Investigations. As explained in the preamble to the final rule, "[t]hese safeguards are intended to ensure that the rights and welfare of children who participate in clinical investigations are adequately protected."[25]

At any stage of development, if data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies; FDA may also halt ongoing clinical studies. The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section

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[23] The IRB is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research. IRBs approve clinical study protocols, which describe the type of people who may participate in the clinical study; the schedule of tests and procedures; the medications and dosages to be studied; the length of the study; the study's objectives; and other details. IRBs make sure that the study is acceptable, that participants have given consent and are fully informed of the risks, and that researchers take appropriate steps to protect patients from harm. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective web page, last updated November 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

[24] 21 CFR § 312.22(a).

[25] Preamble to final rule, "Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products" (78 FR 12937 at 12938, February 26, 2013), https://www.federalregister.gov/documents/2013/02/26/2013-04387/additional-safeguards-for-children-in-clinical-investigations-of-food-and-drug.

505(i)(3) of the FD&C Act; 21 U.S.C. § 355(i)(3)), and FDA's IND regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Generally, a clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation.[26]

b. The Citizen Petition

i. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines and Refrain from Issuing any Future EUA or Approving any Future NDA, or BLA for any COVID-19 Vaccine for all Demographic Groups because the Current Risks of Serious Adverse Events or Deaths Outweigh the Benefits, and Because Existing, Approved Drugs Provide Highly Effective Prophylaxis and Treatment against COVID-19, Mooting the EUAs

Petitioner makes several requests regarding COVID-19 vaccines in the Petition and, in support of these requests, argues that (1) the rates of serious adverse events or deaths outweigh the benefits of these vaccines and (2) approved drugs provide highly effective prophylaxis/treatment against COVID, thereby "mooting" the EUAs. We interpret this as an argument that the authorizations of COVID-19 vaccines to date did not meet the relevant legal standard. Below, we address each of Petitioner's requests and the information provided by Petitioner in support of these requests.

1. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines

In this section, we address Petitioner's request that FDA "revoke all EUAs . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1.

a. EUAs for COVID-19 Vaccines

As noted above in Section II above, FDA may issue an EUA during the COVID-19 public health emergency after FDA concludes that the statutory requirements provided in section 564 of the FD&C Act are met. In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates have been developed. COVID-19 vaccines that have been developed or are currently in development are based on various platforms and include mRNA, DNA, viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

To date, FDA has issued EUAs for three COVID-19 vaccines ("the Authorized COVID-19 Vaccines"), as described in the Scope of Authorization for these COVID-19 vaccines, pursuant

[26] 21 CFR § 312.42(a).

to section 564 of the FD&C Act. Additionally, FDA has expanded the authorized age range for one COVID-19 vaccine.

- On December 11, 2020, FDA issued an EUA for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older.
    - On May 10, 2021, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine to include individuals 12 through 15 years of age.
- On December 18, 2020, FDA issued an EUA for emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.
- On February 27, 2021, FDA issued an EUA for emergency use of Janssen COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.

The Agency issued these EUAs after a thorough evaluation of scientific data regarding the safety, effectiveness, and manufacturing information (which helps ensure product quality and consistency) of these COVID-19 vaccines and after reaching a determination that these vaccines meet the statutory requirements under section 564 of the FD&C Act. This letter incorporates by reference the EUA Review Memoranda for the Authorized COVID-19 Vaccines,[27] which discuss this determination, and the data upon which it was based, in detail as well as the Summary Basis of Regulatory Action for the BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty).[28]

Petitioner argues that the authorizations for these vaccines should be revoked, and that future COVID vaccines should not be authorized or licensed, because (1) "the current risks of serious adverse events or deaths outweigh the benefits," and (2) "existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." We address each of Petitioner's arguments, and data submitted in the Petition in support of these arguments, below.

FDA disagrees with Petitioner's position that the Authorized COVID-19 Vaccines did not meet the statutory standard at the time of authorization, and finds no basis in the information submitted in the Petition, or in any postmarket data regarding these vaccines, to support a revocation of any of these authorizations. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. The

[27] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) https://www.fda.gov/media/151611/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

[28] This letter incorporates by reference FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

known and potential benefits of the Authorized COVID-19 Vaccines continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications. Furthermore**,** as explained below, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19. Accordingly, this request is denied.

b. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines

Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

> (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
> (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
> (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

FDA's guidance entitled *Emergency Use Authorization of Medical Products and Related Authorities* ("EUA Guidance"),[29] notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[30] Regarding the circumstances that would make a revision or revocation appropriate to protect the public health or safety, FDA explains in the EUA guidance that

> Such circumstances may include significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.

[29] Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017 (EUA Guidance), https://www.fda.gov/media/97321/download.
[30] Id. at 28.

EUA guidance at 29.

Thus, in addressing Petitioner's request for FDA to revoke the Authorized COVID-19 Vaccines, we assess whether any of the statutory conditions under which FDA may revoke an EUA are met, namely: (1) whether the circumstances justifying their issuance under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria for their issuance under section 564(c) of the FD&C Act are no longer met, and (3) whether other circumstances make a revision or revocation appropriate to protect the public health or safety.

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccines

As explained above in section II.b., on February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[31] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[32]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the statutory requirements provided in section 564(c) are met. Section 564(b)(2) sets forth the statutory standard for termination of an EUA declaration. An EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Defense) or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is satisfied with respect to the Authorized COVID-19 Vaccines.

Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(A) of the FD&C Act.

ii. The Criteria for The Issuance of the Authorized COVID-19 Vaccines Continue to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the Authorized COVID-19 Vaccines and why, therefore, FDA is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(B) of the FD&C Act.

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[31] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[32] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

1. Serious or life-threatening disease or condition.

Section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the agent(s) referred to in [the HHS Secretary's EUA declaration] can cause a serious or life-threatening disease or condition." FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.[33] In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.[34] On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020.
FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change. Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines.

2. Evidence of Effectiveness

Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2."

FDA issued EUAs for the Authorized COVID-19 Vaccines after determining that, among other things, these products were demonstrated in clinical trials to prevent symptomatic and severe COVID-19 in vaccinated clinical trial subjects.[35] FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. This section addresses Petitioner's arguments regarding the effectiveness of the Authorized COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA's analysis regarding the effectiveness of these vaccines.

After FDA approves a vaccine or authorizes a vaccine for emergency use, the vaccine continues to be studied to determine how well it works under real-world conditions. FDA, CDC, and other federal partners have been assessing, and will continue to assess, COVID-19 vaccine

[33] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html.
[34] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.
[35] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, https://www.fda.gov/media/146338/download.

effectiveness under real-world conditions. Such evaluations will help us understand if vaccines are performing as expected outside the more controlled setting of a clinical trial.

Petitioner raises concerns regarding the post-market effectiveness of the Authorized COVID-19 Vaccines (Petition at 6). Petitioner points to CDC-reported "breakthrough cases" to suggest that the Authorized COVID-19 Vaccines are not effective and argues that the EUAs for the Authorized COVID-19 Vaccines should therefore be revoked because the current risks of these vaccines outweigh their benefits. This perspective fails to recognize several important points regarding the concept of breakthrough cases and regarding the CDC publication cited in the Petition.

First, we note that the Letters of Authorization for the Authorized COVID-19 Vaccines require EUA-holders to report to VAERS "cases of COVID-19 that result in hospitalization or death, that are reported to [the EUA holder]."[36] Thus, the possibility that individuals who received one of the Authorized COVID-19 Vaccines could develop breakthrough COVID-19 cases was recognized by FDA when the Agency evaluated the EUA requests for these vaccines and determined that their known and potential benefits outweigh their known and potential and risks.

Second, the Authorized COVID-19 Vaccines are indicated to prevent *symptomatic* COVID-19,[37] not to prevent SARS-CoV-2 infection. Over 353 million doses of COVID-19 vaccines have been administered in the United States[38] and FDA's ongoing post authorization monitoring informs us that the known and potential benefits continue to outweigh the known and potential risks. Additionally, CDC's post-authorization data regarding the Authorized COVID-19 Vaccines continues to support FDA's conclusion that these vaccines prevent *symptomatic* COVID-19.[39]

Third, a vaccine does not need to be 100% effective in preventing the target disease in order to meet the licensure or EUA standard. It is expected that some vaccinated individuals will contract the target disease despite having been vaccinated against it. No FDA licensed or authorized vaccine is 100% effective, but scientific data has nevertheless demonstrated that vaccinations have been a very effective approach to protecting the public's health in the United States.[40]

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[36] Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144413/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144637/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/146304/download.

[37] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, https://www.fda.gov/media/146338/download.

[38] CDC, COVID Data Tracker Weekly Review, Interpretive Summary for August 13, 2021, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

[39] CDC, COVID-19 Vaccine Effectiveness Research, https://www.cdc.gov/vaccines/covid-19/effectiveness-research/protocols.html.

[40] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

Similarly, a COVID-19 vaccine need not be 100% effective in preventing symptomatic COVID-19, or even close to 100% effective in doing so, in order to have a significant effect in altering the course of the COVID-19 pandemic. As FDA noted in its June 2020 Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, ("The Vaccine Development and Licensure Guidance") "[t]o ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%."[41] This statistical consideration provided in the Vaccine Development and Licensure Guidance reflects FDA's assessment that a vaccine with at least 50 percent efficacy would have a significant impact on disease, both at the individual and societal level.
Finally, we note that Petitioner refers to "CDC-reported" breakthrough cases in support of its argument that there are effectiveness concerns with the Authorized COVID-19 Vaccines but fails to acknowledge that CDC reported a set of breakthrough cases that includes a large proportion of *asymptomatic* individuals who tested positive for SARS-CoV-2. Petitioner thus applies a narrower definition of the term "breakthrough case" to a set of cases than CDC has in its COVID-19 Vaccine Breakthrough Case Investigation.[42] Petitioner refers to breakthrough cases in which vaccinated individuals "fall ill and potentially transmit the virus" (Petition at 6) and states that "CDC reported over 9,000 'breakthrough cases' and 132 COVID-caused deaths among vaccinated people." Petition at 6.

CDC's objective in the COVID-19 Vaccine Breakthrough Case Investigation is to[43] ensure the COVID-19 vaccines are working as expected and to "identify patterns or trends" in:

- Patients' characteristics, such as age or underlying medical conditions
- The specific vaccine that patients received
- Whether a specific SARS-CoV-2 variant caused the infections"[44]

The objective of this investigation is not simply to count symptomatic COVID-19 cases. Currently, COVID-19 cases are increasing again in nearly all states. The highest rate of COVID-19 case spread is in areas with low vaccination rates.[45]

Petitioner's submitted data regarding CDC-reported "breakthrough cases" therefore does not present new data or information that the Agency has not previously considered regarding the effectiveness of the Authorized COVID-19 Vaccines. Available data regarding effectiveness of

[41] Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, June 2020, at 14, https://www.fda.gov/media/139638/download.
[42] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.
[43] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.
[44] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.
[45] "As of July 22 [2021], 35% of U.S. counties are experiencing high levels of community transmission. COVID-19 cases are on the rise in nearly 90% of U.S. jurisdictions, and we are seeing outbreaks in parts of the country that have low vaccination coverage." CDC, COVID Data Tracker Weekly Review, Interpretive Summary for July 23, 2021, available at https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

the Authorized COVID-19 Vaccines continues to support the conclusion that these vaccines may be effective in preventing COVID-19. FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." Petitioner argues that the current risks of serious adverse events or deaths associated with the Authorized COVID-19 Vaccines outweigh the benefits of COVID-19 vaccines. This section addresses Petitioner's arguments regarding the safety of COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA's analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

FDA issued EUAs for the Authorized COVID-19 Vaccines after reaching a determination regarding each of these vaccines that, among other things, the known and potential benefits of the vaccine, when used to prevent COVID-19, outweigh its known and potential risks.[46] FDA is not aware of any data that changes this determination, nor has Petitioner provided any such data in the Petition. The known and potential benefits of the Authorized COVID-19 Vaccines, when used to prevent COVID-19, continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications.

Petitioner raises numerous concerns regarding safety of the Authorized COVID-19 Vaccines (Petition at 2-6) and asserts that the EUAs for the Authorized COVID-19 Vaccines should be revoked due in part to these safety concerns. For reasons explained below, FDA disagrees with Petitioner's assertions regarding the safety of the Authorized COVID-19 Vaccines.

As an initial matter, we note that the Petition discusses several assertions made by CDC and requests that have been directed to CDC. For requests intended for CDC, you should contact CDC directly.

a. Petitioner's Claims Regarding VAERS Data

[46] For an extensive discussion of FDA's analysis of the clinical trial data regarding the risks and benefits of each of the authorized COVID-19 Vaccines, *see* FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 49, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 55, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 59, https://www.fda.gov/media/146338/download. *See also*, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 38, https://www.fda.gov/media/148542/download.

In arguing that the Authorized COVID-19 Vaccines should be revoked due, in part, to safety concerns, Petitioners assert that "Vaccine Adverse Event Reporting System (VAERS) data reveal unprecedented levels of deaths and other adverse events since the FDA issued Emergency Use Authorizations (EUAs) for three COVID vaccines. As of May 10, 2021, VAERS reported 4,434 deaths of people who received at least one COVID vaccination." As an initial matter, we note that VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. VAERS is not designed to assess whether a reported adverse event was caused by a vaccine. This section explains vaccine safety surveillance, including VAERS, in greater detail below.

Regarding the number of VAERS reports submitted for the Authorized COVID-19 Vaccines, this figure can be attributed to multiple factors. First, we note that a large number of COVID-19 vaccine doses have been administered in the United States and that certain adverse event reporting by vaccination providers is *required* for the Authorized COVID-19 Vaccines. As of August 13, 2021, over 353,000,000 doses of the Authorized COVID-19 Vaccines have been administered.[47] We note that the crude number of VAERS reports of death is extremely small compared to the to the large number of people who have been vaccinated. The VAERS reporting rate for deaths (which is the number of VAERS death reports received out of the number of individuals vaccinated) for the Authorized COVID-19 Vaccines is actually very low (6,490 reports of death out of 346 million doses administered (0.0019%) as of August 2, 2021).[48] Petitioner's assertion fails to account for this fact.

For licensed vaccines, healthcare providers are legally required under 42 USC 300aa-25 to report to VAERS two categories of adverse events: "[a]ny adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs *within the specified time period after vaccination* [and] [a]n adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine"[49] Vaccine manufacturers are also required to report to VAERS all adverse events that come to their attention.[50]
Under the EUAs for the Authorized COVID-19 Vaccines, however, vaccination providers are required to report to VAERS serious adverse events following vaccination with the Authorized COVID-19 Vaccines, "irrespective of attribution to vaccination" and without a specified time period after vaccination.[51] Another contributing factor is the v-safe system,[52] which is a new CDC smartphone-based active-surveillance system in which participants who have been

[47] CDC, COVID Data Tracker, COVID-19 Vaccinations in the United States, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.
[48] CDC, Selected Adverse Events Reported after COVID-19 Vaccination, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
[49] VAERS, Frequently Asked Questions, https://vaers.hhs.gov/faq.html (emphasis added).
[50] 21 CFR 600.80. See also VAERS, Frequently Asked Questions, https://vaers.hhs.gov/faq.html.
[51] Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144413/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144637/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/146304/download.
[52] CDC, v-safe Overview, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html.

vaccinated may voluntarily enroll. This system was developed for the COVID-19 vaccination program. V-safe sends text messages and web surveys to participants who can report side effects following receipt of a COVID-19 vaccine. If a participant indicates through the v-safe surveys that he or she required medical care at any time, CDC calls the participant to complete a report through VAERS. This system is unique to COVID-19 vaccines and may be contributing to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines.
Finally, another potential factor is the concept of "stimulated reporting."[53] Because of extensive media coverage and awareness of the public health emergency – and of the Authorized COVID-19 Vaccines and their reported side effects –vaccine recipients, health care providers, and others are more likely to report adverse events for the Authorized COVID-19 Vaccines than for other vaccines that have been widely available for longer periods of time. Additionally, one of the articles submitted by Petitioner in support of their argument actually provides support for this explanation for the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The article notes "[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been *misinterpreted as actual increases in incidence of adverse events and vaccine related risk*."[54] Petitioner's argument regarding VAERS data for the Authorized COVID-19 Vaccines is unavailing because it fails to account for the factors outlined above.

In addressing Petitioner's assertion regarding VAERS claims, this section addresses the extensive vaccine safety surveillance efforts, in addition to VAERS, that are in place for the Authorized COVID-19 Vaccines.[55] FDA is monitoring the safety of the Authorized COVID-19 Vaccines through both passive and active safety surveillance systems. FDA is doing so in collaboration with the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the Department of Veterans Affairs (VA), and other academic and large non-government healthcare data systems.

In addition, FDA participates actively in ongoing international pharmacovigilance efforts, including those organized by the International Coalition of Medicines Regulatory Authorities

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[53] We note that an article submitted by Petitioner in support of their arguments regarding VAERS acknowledges this concept: "Like all spontaneous public health reporting systems, VAERS has limitations. VAERS is subject to reporting bias, including underreporting of adverse events – especially common, mild ones– and stimulated reporting, which is elevated reporting that might occur in response to intense media attention and increased public awareness, such as during the 2009 H1N1 pandemic influenza vaccination program" Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/. See also "The number of reports and reporting rate following 2009-H1N1 vaccination were higher than following 2009–2010 seasonal influenza vaccines for all age groups. These findings, however, should be interpreted in light of the publicity around the 2009-H1N1 vaccine and efforts to increase reporting to VAERS. Heightened public awareness and stimulated reporting likely enhanced reporting to VAERS. Furthermore, although 2009-H1N1 was licensed similarly to seasonal influenza vaccines, it was likely perceived as a 'new' vaccine by the public and susceptible to the known tendency (i.e., the Weber effect) for adverse events to be reported more frequently following newly licensed products." Vellozzi, et al., Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010, Vaccine (Oct. 21, 2010), https://www.sciencedirect.com/science/article/pii/S0264410X10013319.

[54] Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/ (emphasis added).

[55] FDA, COVID-19 Vaccine Safety Surveillance, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance.

(ICMRA) and the World Health Organization (WHO). These efforts are in addition to the pharmacovigilance efforts being undertaken by the individual manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of the art technologies has been implemented. As part of our efforts to be transparent about our COVID-19 vaccine safety monitoring activities, FDA is posting summaries of the key safety monitoring findings on the FDA website. [56]

i. Vaccine Safety Surveillance

Passive Surveillance

VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events, as providers of COVID-19 vaccines are required to report serious adverse events to VAERS.
As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." VAERS reports generally cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. If the VAERS data suggest a possible link between an adverse event and vaccination, the relationship may be further studied in a controlled fashion.[57]

Anyone can make a report to VAERS, including vaccine manufacturers, private practitioners, state and local public health clinics, vaccine recipients, and their parents or caregivers. Surveillance programs like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation.

VAERS is not designed to assess causality. It is often difficult to determine with certainty if a vaccine caused an adverse event reported to VAERS. Many events that occur after vaccination can happen by chance alone. Some adverse events are so rare that their association with a vaccine is difficult to evaluate. In addition, we often receive reports where there is no clear clinical diagnosis. FDA draws upon multiple sources of data and medical and scientific expertise to assess the potential strength of association between a vaccine, including COVID-19 vaccines, and a possible adverse event.

If VAERS monitoring suggests that a vaccine might be causing a health problem, additional scientifically rigorous studies or investigations can be performed by FDA and CDC. Monitoring and analysis of VAERS reports typically includes daily in-depth medical review of all serious reports, statistical data mining techniques, and epidemiological analysis. We look for patterns and similarities in the onset timing and clinical description. We review published literature to

[56] FDA, COVID-19 Vaccine Safety Surveillance, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance
[57] FDA, VAERS Overview, https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview.

understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure or pre-authorization data and any other post-marketing studies that have been conducted. We also consider "background rate," meaning the rate at which a type of adverse event occurs in the unvaccinated general population. When necessary, we discuss the potential adverse event with our federal and international safety surveillance partners. We also carefully evaluate unusual or unexpected reports, as well as reports of "positive re-challenges" (adverse events that occur in the same patient after each dose received). When there is sufficient evidence for a potential safety concern, we may proceed to conduct large studies, and we may coordinate with our federal, academic, and private partners to further assess the potential risk after vaccination. In addition, when potential safety issues arise, they are often presented to various U.S. government advisory committees, including the Vaccines and Related Biological Products Advisory Committee, the Advisory Committee on Immunization Practices (ACIP), and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization. Federal agencies that assist in population-based vaccines safety studies include the CDC, Centers for Medicaid and Medicare (CMS), the Department of Defense (DoD), and the Indian Health Services (IHS). In addition, we generally communicate and work with international regulatory authorities and international partners to conduct studies in vaccine safety.

Active Surveillance

Active surveillance involves proactively obtaining and rapidly analyzing information related to millions of individuals and recorded in large healthcare data systems to verify safety signals identified through passive surveillance or to detect additional safety signals that may not have been reported as adverse events to passive surveillance systems. FDA is conducting active surveillance using the Sentinel BEST (Biologics Effectiveness and Safety) System and the CMS system, and is also collaborating with other federal and non-federal partners.

BEST

To elaborate further, the BEST system,[58] which is part of the Sentinel initiative,[59] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The linked claims-EHR database makes it possible to study the safety of vaccines in sub-populations with pre-existing conditions or in pregnant women. The major partners for BEST currently are Acumen, IBM Federal HealthCare, IQVIA, and Columbia University and many affiliated partners such as MedStar Health, BlueCross BlueShield of

[58] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
[59] FDA's Sentinel Initiative, https://www.fda.gov/safety/fdas-sentinel-initiative.

America, the Observational Health Data Sciences and Informatics (OHDSI), OneFlorida, University of California and several others.[60]

Using BEST, CBER plans to monitor about 15 adverse events[61] that have been seen with the deployment of previous vaccines but have yet to be associated with a safety concern for an authorized COVID-19 vaccine at this time. CBER further plans to use the BEST system to conduct more in-depth analyses should a safety concern be identified from sources such as VAERS.

CMS

FDA has worked over the past several years with CMS to develop capabilities for routine and time-sensitive assessments of the safety of vaccines for people 65 years of age and older using the Medicare Claims database.[62] Because it was already in place, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.[63]

During the current pandemic, FDA, CMS, and CDC have already used the Medicare data to publish a study showing that frailty, comorbidities, and race/ethnicity were strong risk factors of COVID-19 hospitalization and death among the U.S. elderly.[64]

VSD

In addition, the Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. As noted on the CDC's

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[60] To confirm the utility of the BEST system for situations such as COVID-19 vaccine surveillance, a test case was conducted. This study aimed to replicate a previous study by the CDC's Vaccine Safety Datalink (VSD) (Klein et al. Pediatrics 2010) that examined the databases and analytic capabilities of the new system. The objective of this study was to test the new system's ability to reproduce the increased risk of febrile seizures in children receiving the first dose of measles-mumps-rubella-varicella (MMRV) vaccine, compared to that of MMR and varicella vaccines separately but on the same day. The results of the study met the objectives and demonstrated the ability of the BEST Initiative data network to run a complex study protocol at multiple sites using a distributed data network and the Observational Medical Outcomes Partnership Common Data Model (organizing disparate data sources into the same database design using a common format).

[61] Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, Draft Protocol (December 31, 2020), https://www.bestinitiative.org/wp-content/uploads/2021/01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf.

[62] CMS, Standard Analytical Files (Medicare Claims) – LDS, https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles.

[63] As one example of the capabilities of this system, FDA, CMS, and CDC evaluated the risk of Guillain-Barré syndrome (GBS) following influenza vaccination after CDC's Vaccine Safety Datalink, identified safety signals suggesting an increased risk of GBS following high-dose influenza vaccinations and Shingrix vaccinations during the 2018-2019 influenza season. CBER, CDC, and CMS formed working groups in February 2019 to refine these safety signals in the CMS data.

[64] Hector S Izurieta, David J Graham, Yixin Jiao, Mao Hu, Yun Lu, Yue Wu, Yoganand Chillarige, Michael Wernecke, Mikhail Menis, Douglas Pratt, Jeffrey Kelman, Richard Forshee, Natural History of Coronavirus Disease 2019: Risk Factors for Hospitalizations and Deaths Among >26 Million US Medicare Beneficiaries, The Journal of Infectious Diseases, Volume 223, Issue 6, 15 March 2021, Pages 945–956, https://doi.org/10.1093/infdis/jiaa767 https://academic.oup.com/jid/article/223/6/945/6039057.

webpage, the VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization.

The VSD uses electronic health data from each participating site. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays. The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.

The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.[65]

In summary, in collaboration and coordination with several different partners, FDA has assembled passive surveillance systems - including VAERS - and active surveillance systems that can detect and refine safety findings with the Authorized COVID-19 Vaccines in a relatively rapid manner. These systems can also potentially be leveraged to assess safety in specific subpopulations and to assess vaccine effectiveness.

ii. Articles Submitted in Petition Regarding Vaccine Surveillance

We note at the outset that Petitioner raises concerns regarding the methodology by which CDC calculated rates of anaphylactic adverse events post-vaccination. Such concerns are best directed to CDC and are outside the scope of FDA's Petition response.

Regarding Petitioner's contention that a low percentage of adverse events have been reported to VAERS and that therefore "the safety of COVID vaccines is considerably worse than it currently appears" (Petition at 4), as explained in detail above in this section, VAERS is only one part of a multi-tiered vaccine safety surveillance system, so the information derived from VAERS reports does not represent the full extent of vaccine safety information being monitored by FDA and its federal partners.

Specifically, Petitioner cites to three studies in support of the argument that "[g]iven that only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system, according to Lazarus et al., the high number of adverse events and deaths following COVID vaccines is alarming." Petition at 5. The articles cited by Petitioner in support of this contention do not support Petitioner's position that, due to underreporting of adverse events, the rate of reported adverse events associated with COVID-19 vaccination is low in comparison to the actual rate of adverse events. As discussed above in this section, there are several factors unique to the surveillance of the Authorized COVID-19 Vaccines that have

[65] *See, e.g.,* CDC, White Paper on the Safety of the Childhood Immunization Schedule, Vaccine Safety Datalink, available at https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf.

contributed to the number of VAERS reports submitted for these vaccines. Petitioner's argument that adverse events associated with the Authorized COVID-19 Vaccines are underreported because of the figures presented in the articles cited fail to account for any of those factors that are unique to the Authorized COVID-19 Vaccines.

Petitioner cites to a publication from the Agency for Healthcare Research and Quality (Lazarus et al.) in support of the argument that deaths and adverse events associated with the Authorized COVID-19 Vaccines are underreported because "only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system" (Petition at 5), and therefore the actual rate of COVID-19 Vaccine adverse events is significantly higher than reported.[66] As an initial matter, we note that the language cited from the Lazarus article is referring to adverse event reporting for drugs and vaccines, not just vaccine adverse events reported to VAERS.[67] Furthermore, as explained in detail above, several factors have contributed to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The issues raised in this article regarding underreporting of drug adverse event reporting are not directly relevant to the claims Petitioner makes regarding adverse event reporting for the Authorized COVID-19 Vaccines. The article was published in 2010 and does not consider the numerous factors outlined above regarding reporting of adverse events following COVID-19 vaccination.

Petitioner cites to a journal article in the publication *Vaccine*[68] regarding VAERS safety monitoring in support of their argument that adverse event reports for the Authorized COVID-19 Vaccines are underreported. This article generally discusses the limitations of VAERS and passive surveillance, which are well-understood by the FDA and which are discussed in this letter. Additionally, this article notes "[p]erhaps the two most common misconceptions about VAERS are that temporally associated reports represent true adverse reactions caused by vaccination, and that VAERS reports equate to rates of adverse events or indicate risk of adverse events associated with vaccination."[69] This statement from the article demonstrates the flaws underlying Petitioner's claims that the Authorized COVID-19 Vaccines are unsafe due to the number of serious adverse events reported to VAERS following administration of these vaccines. Additionally, the article notes "[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been misinterpreted as actual increases in incidence of adverse events and vaccine related risk."[70] Thus, the article cited by Petitioner directly contradicts Petitioner's claims regarding the safety of the Authorized COVID-19 Vaccines based on the number of VAERS adverse event reports associated with these vaccines.

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[66] Lazarus et al., Electronic Support for Public Health-Vaccine Adverse Event Reporting System, Agency for Healthcare Research and Quality, HHS (Sept. 30, 2010), https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system.
[67] Id. at 6.
[68] Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/.
[69] Id. at 9.
[70] Id.

Finally, Petitioner also cites to a journal article in the American Journal of Public Health.[71] This article does not raise issues that have not already been addressed in this letter's discussion of safety surveillance. For instance, the article notes that passive surveillance has several limitations, specifically, passive surveillance may involve underreporting of adverse events, and passive surveillance data is not adequate to determine causation. Additionally, this article notes that passive surveillance can provide valuable information, "[n]evertheless, if reporting is reasonably consistent, it may be possible to detect changes in trends of known common adverse events."[72]

Therefore, the articles submitted by Petitioner do not present data or information regarding the Authorized COVID-19 Vaccines that change the Agency's analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

Petitioner further asserts that extensive safety information regarding vaccines is inaccessible to the public ("the VAERS database is the only safety database to which the public has access. The government withholds extensive safety information from the public despite having at least ten additional data sources and expert consultants to analyze these data . . . ." Petition at 2.). This contention represents a misunderstanding by Petitioner of the sources of data analyzed by FDA and its federal partners, and of the types of information available to the public.
As noted above, Petitioner's questions regarding databases operated by other federal partners, such as DOD, CMS, CDC, VA, should be directed to those federal entities. Regarding FDA's BEST system, Petitioner erroneously claims that the public does not have access to the information on this system. As noted above, the BEST system,[73] which is part of the Sentinel initiative,[74] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The system is not intended to be a source of raw EHR data. Instead, as explained on FDA's webpage describing the BEST system, the purpose of the BEST system is to: (1) build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products; and (2) develop innovative methods to utilize electronic health records (EHR) effectively and establish automated adverse events reporting, utilizing natural language processing and artificial intelligence.[75] BEST does not have access to the raw, identifiable data. BEST data partners analyze the raw data per publicly posted protocols and send the results in aggregated form to BEST for review. The information is summarized in either final reports, manuscripts or public presentations. BEST publicly posts study protocols of surveillance activities on the BEST site with open public comments regarding the protocols, final reports and manuscripts as well as communication on CBER safety site and public meetings, e.g., VRBPAC, where appropriate. These protocols delineate the scientific approach to analyzing the raw data, where in the raw form is of limited utility to the public, to

[71] S. Rosenthal and R. Chen, The reporting sensitivities of two passive surveillance systems for vaccine adverse events, American Journal of Public Health (Dec. 1995), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1615747/.
[72] Id.
[73] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
[74] FDA's Sentinel Initiative, https://www.fda.gov/safety/fdas-sentinel-initiative.
[75] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.

generate information on vaccine safety. The final reports and manuscripts summarize the information and conclusions inferred from well-conducted surveillance studies.

iii. FDA Has Responded to Safety Signals Related to the Authorized COVID-19 Vaccines by Extensively Reviewing Data, Updating the Authorized Labeling, and Communicating to the Public

Petitioner further asserts that "FDA and CDC have not responded to these data by issuing any warnings or restricting the use of these vaccines." Petition at 2. This assertion is inaccurate. As explained in detail above, FDA and its federal partners, including CDC, have closely monitored post-market safety data regarding the Authorized COVID-19 Vaccines. FDA has worked to identify and investigate serious adverse events occurring in people after receiving the Authorized COVID-19 Vaccines, and to communicate these risks to the public and revise the authorized labeling to reflect these risks in a timely fashion.[76] The surveillance systems that are in place to monitor the safety of COVID-19 vaccines authorized for emergency use are working, as demonstrated by FDA's and CDC's work to identify and investigate these serious adverse events in a timely manner.

Adverse events reported to VAERS following administration of one of the authorized COVID-19 vaccines are reviewed to assess possible safety concerns. Such review of VAERS data regarding the authorized COVID-19 vaccines has been conducted since these vaccines were authorized. Such review has prompted the Agency to take action with respect to the currently authorized COVID-19 vaccines:

- On April 13, 2021, FDA and CDC recommended a pause in the use of the Janssen COVID-19 vaccine following six VAERS reports in the U.S. of thrombosis with thrombocytopenia.[77] The FDA and CDC thoroughly reviewed VAERS and other post-authorization information and data related to the Janssen COVID-19 vaccine during the recommended pause. This review included two meetings of ACIP. Following a thorough safety review, FDA determined that the available data show that the Janssen COVID-19 vaccine's known and potential benefits outweigh its known and potential

[76] Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, https://www.fda.gov/media/146304/download; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144413/download; Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144637/download.

[77] We note that Petitioner mentions that Denmark, among other nations, has "banned" the Janssen COVID-19 vaccine. To the extent Petitioner relies on this ban as support for Petitioner's request that FDA revoke the EUA for this vaccine, we note that Denmark and other nations' actions with respect to the use of this vaccine are outside purview of FDA's work, so we cannot comment on decisions they make under their public health regulatory framework.

risks in individuals 18 years of age and older. As a result of this review, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include a Warning pertaining to the risk of thrombosis with thrombocytopenia. The Fact Sheet for Recipients and Caregivers was also updated to include information about these serious adverse events. The FDA and CDC conducted extensive outreach to providers and clinicians to ensure they were made aware of the potential for these adverse events and could properly recognize and manage thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine.

- On June 25, 2021, following review of VAERS reports, FDA required revisions to the authorized labeling for the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine to add a warning regarding the suggested increased risks of myocarditis and pericarditis. This update to the authorized labeling for these vaccines followed an extensive review of information and the discussion by CDC's ACIP meeting on June 23, 2021. As of July 26, 2021, the FDA and the Centers for Disease Control and Prevention (CDC) have received 1,194 reports of myocarditis or pericarditis occurring among people ages 30 and younger who received either Moderna or Pfizer-BioNTech COVID-19 vaccines, particularly following the second dose.[78] Through follow-up, including medical record reviews, the FDA and CDC had confirmed 699 cases of myocarditis or pericarditis.[79]
- On July 13, 2021, FDA required revisions to the vaccine recipient and vaccination provider fact sheets for the Janssen COVID-19 Vaccine to include information pertaining to a suggested increased risk of Guillain-Barré Syndrome (GBS) during the 42 days following vaccination. Based on an analysis of Vaccine Adverse Event Reporting (VAERS) data, at that time, there had been 100 reports of presumptive GBS following vaccination with the Janssen vaccine after approximately 12.5 million doses administered. Of these reports, 95 of them were serious and required hospitalization. There was one reported death. As noted in the Janssen Fact Sheet for Healthcare Providers Administering Vaccine, because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Each year in the United States, an estimated 3,000 to 6,000 people develop GBS. Most people fully recover from the disorder. FDA publicly presented this issue, and information regarding these 100 reports of presumptive GBS, to the ACIP on July 22, 2021.[80]

During each of these post-authorization reviews and labeling changes, the FDA has evaluated the available post-authorization information for the authorized COVID-19 Vaccines and continues to find the known and potential benefits clearly outweigh the known and potential risks.

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[78] CDC, COVID-19 Reported Adverse Events, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
[79] Id.
[80] FDA, CDC ACIP Meeting Presentation, Guillain-Barré Syndrome (GBS) after Janssen COVID-19 Vaccine: Vaccine Adverse Event Reporting System (VAERS), July 22, 2021, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/02-COVID-Alimchandani-508.pdf.

iv. Petitioner's Claims Regarding Anaphylaxis

Petitioner cites to a study of acute allergic reactions to mRNA COVID-19 vaccines in support of their argument that adverse event rates for COVID-19 vaccines have been miscalculated by CDC.[81] As stated above, questions relating to CDC are best directed to that Agency. We note, however, that this journal article states, immediately after the sentence quoted by Petitioner, "[h]owever, the overall risk of anaphylaxis to an mRNA COVID-19 vaccine remains extremely low and largely comparable to other common health care exposures. Although cases were clinically compatible with anaphylaxis, the mechanism of these reactions is unknown." The paper further states, in describing the limitations of the study, that "[a] northeastern US cohort may not be generalizable." Thus, Petitioner is inappropriately generalizing the results of this study in an attempt to compare the results to the CDC's reported data and conclude that the safety of COVID vaccines is "considerably worse than it currently appears." Petition at 4.

Additionally, we note that the authorized labeling for all the Authorized COVID-19 vaccines already contain warnings regarding the risk of anaphylaxis as a potential adverse event. Thus, the risk of anaphylaxis is a potential safety issue FDA is already aware of, and Petitioner's argument, and the article submitted in support of this argument, does not change FDA's conclusions regarding the safety of the Authorized COVID-19 vaccines.

v. Animal Toxicology and Pharmacokinetic Studies of COVID-19 Vaccines

Petitioner raises concerns regarding FDA's vaccine safety assessment. Specifically, Petitioner states that other "problems with vaccine safety assessment *may exist* because of inadequate animal toxicology and pharmacokinetic studies of COVID vaccines." Petition at 5; emphasis added. As an initial matter, we note that Petitioner's concerns regarding the vaccine safety assessment for COVID-19 vaccines involves speculation regarding whether problems actually exist ("problems with vaccine safety assessment *may exist* . . ."), and Petitioner fails to point to any specific problems that result or may result from the allegedly inadequate studies. Regarding Petitioner's claims, in general, when evaluating the safety data regarding a vaccine, FDA considers data from animal studies (if such pre-clinical studies were performed) as one part of the full body of evidence regarding the vaccine. In addition to data from animal studies, if available, FDA evaluates data from in vitro studies and conducts a safety assessment of data from clinical studies.

Thus, although Petitioner raises several concerns and cites to several articles regarding risks of COVID-19 vaccination, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Therefore, the

[81] Blumenthal KG, Robinson LB, Camargo CA, et al., Acute Allergic Reactions to mRNA COVID-19 Vaccines, JAMA. 2021;325(15):1562–1565. doi:10.1001/jama.2021.3976, https://jamanetwork.com/journals/jama/fullarticle/2777417.

criterion under section 564(c)(2)(B) continues to be met with respect to the Authorized COVID-19 Vaccines.

4. No Alternatives

As noted above, Petitioner requests that "FDA should revoke all EUAs and refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1. Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]."[82] To the extent Petitioner's contention can be interpreted as an argument that there are adequate, approved, available drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no "adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19 is not met), this argument is erroneous.

As explained in the Decision Review Memoranda for the Authorized COVID-19 Vaccines, at the time each COVID-19 vaccine EUA was issued, there were no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population because no vaccine or other medical product was the subject of an approved marketing application for prevention of COVID-19.[83] This is still true today, with the exception of the BLA for BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty), which is now approved for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect. This EUA will continue to cover individuals 12 through 15 years of age, to cover the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and to cover individuals 16 years of age and older until sufficient approved vaccine can be manufactured and distributed. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Although FDA has approved one new drug application (NDA) for remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization, this drug is not for prevention of COVID-19. Several other therapies are currently available under EUA, but not FDA approved, for treatment of COVID-19, and one is available under EUA, but not FDA approved, for post-exposure prophylaxis in a limited population. These products that are available under EUA are not considered "approved" products for purposes of section

[82] The term "approved," for purposes of section 564(c) of the FD&C Act, means a product is approved, licensed, or cleared by FDA under section 505, 510(k), or 515 of the FD&C Act or section 351 of the PHS Act, as applicable, and this term is indication-specific. *See*, section 564(a)(2) of the FD&C Act. *See also,* EUA guidance at 3.
[83] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, https://www.fda.gov/media/146338/download.

564(c)(3) because they are not the subject of an approved marketing application (i.e., they are not approved under an NDA or BLA).

Thus, Petitioner's assertion that the EUAs for the Authorized COVID-19 Vaccines are "mooted" by the existence of drugs approved to prevent COVID-19 is incorrect.

5. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[84]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of any of the Authorized COVID-19 Vaccines appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the three authorized COVID-19 vaccines because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of these products, when used to prevent COVID-19, outweigh the known and potential risks of these products, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19.

As described in detail in section III.b.i.1.b above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

[84] EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.[85]

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Authorized COVID-19 Vaccines, to support a revocation of any of these EUAs, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances.

FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the any of the Authorized COVID-19 Vaccines. Accordingly, as noted above, we deny Petitioner's request for FDA to "revoke all EUAs . . . for any COVID vaccine for all demographic groups because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."

2. Petitioner's Request to Refrain from Granting any Future EUA for a COVID-19 Vaccine for any Population Because Approved Drugs Exist for COVID-19 Prevention

Petitioner also requests in the Petition that FDA "refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."[86] Petition at 1.

Petitioner has provided no evidence that would provide a basis for FDA to conclude that no future COVID-19 vaccine candidate could meet the EUA standard. Indeed, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition.

Additionally, as explained above in section III.b.i.1.b. of this letter, to the extent Petitioner's contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no "adequate, approved, and available alternative" could not be met), this

[85] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12 -15 Years of Age (May 10, 2021), Section 4.6, EUA Prescribing Information and Fact Sheets, https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151611/download.

[86] FDA authorization of an EUA request is not FDA approval. FDA does not "approve" an EUA request. Rather, FDA *authorizes* the emergency use of a product following review of data and information submitted in an EUA request.

argument fails. Should FDA receive future requests for EUAs for COVID-19 vaccine candidates, FDA would consider such requests on a case-by-case basis.[87] Accordingly, Petitioner's request is denied.

3. Petitioner's Request to Refrain from Approving any Future NDA for any COVID-19 Vaccine for any Population

Petitioner's request regarding "any future…NDA … for any COVID Vaccine for all demographic groups" is moot because vaccines are biological products subject to licensure under the PHS Act and are not subject to approval under section 505 of the FD&C Act.

4. Petitioner's Request to Refrain from Licensing any Future BLA for any COVID-19 Vaccine for any Population

Petitioner requests that FDA "refrain from approving any future . . . BLA for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1. To the extent this request can be interpreted as asserting that the risks of serious adverse events or deaths associated with any COVID-19 vaccine would necessarily outweigh the benefits of any COVID-19 vaccine and therefore FDA should refrain from approving any BLA for any COVID-19 vaccine, this section explains why this argument is unavailing and why we are denying Petitioner's request.

To the extent this request can be interpreted as *also* asserting, in addition to the assertion above, that, because approved drugs provide effective prophylaxis and treatment of COVID-19, the approval of a BLA for a COVID-19 vaccine would be "moot," this section explains why such a position is flawed and why FDA is not granting this request.

a. Petitioner's Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits

Petitioner requests that FDA "refrain from approving any future BLA . . . for any COVID vaccine for all demographic groups" because the risks of serious adverse events or deaths associated with any COVID-19 vaccine outweigh the benefits of any COVID-19 vaccine. Petitioner has provided no evidence that would provide a basis for FDA to conclude that no COVID-19 vaccine could meet the BLA approval standard, however. Indeed, FDA has now approved a BLA for BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) because, among other things, the data and information in the application demonstrated the safety and effectiveness of the vaccine.[88] Thus, Petitioner's request that FDA refrain from approving any BLAs for COVID-19 vaccines is denied.

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[87] FDA has issued guidance describing factors the Agency intends to use in determining how to prioritize EUA requests for COVID-19 vaccine candidates. See October 2020 Guidance at 5 (citing EUA Guidance at 18-20).
[88] See FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

In Appendix I to this letter, we have provided additional background information about FDA's regulatory framework for the review of vaccine BLAs.

b. Petitioner's Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits and because Currently-Approved Drugs are Effective in Preventing COVID-19

To the extent Petitioner is arguing that FDA should *also* refrain from approving a BLA for any COVID-19 vaccine because of the existence of FDA-approved drugs that are effective in preventing COVID-19, this argument is unavailing. As described above in section III.b.i.1, there are no FDA-approved drugs that are effective in preventing COVID-19 (other than BioNTech'sCOVID-19 vaccine [COVID-19 Vaccine, mRNA; Comirnaty], which is now approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.).

For the reasons outlined in this section, FDA denies Petitioner's requests to refrain from licensing any BLAs for a COVID-19 vaccine.

ii. Petitioner's Requests Regarding COVID-19 Vaccines in Children

1. Request to Immediately Refrain from Allowing COVID-19 Vaccine Trials to Include Pediatric Subjects

In the Petition, Petitioner requests that FDA "immediately refrain from allowing minors to participate in COVID vaccine trials . . . ." Petition at 1. To the extent that the Petition can be interpreted to request that FDA suspend any COVID-19 vaccine clinical trial that includes pediatric subjects, this section explains why FDA is not at this time ordering that these clinical trials be suspended.

As explained above in section III.a., with certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND submitted to FDA by the sponsor. FDA's review of an IND includes a review of the study protocol which describes, among other things, the design of the clinical study, including the identified endpoints and methods for assessing the safety and effectiveness of the investigational product. The Petition requests that FDA adopt a universal approach toward all clinical trials of COVID-19 vaccines. Under FDA's regulations, however, the Agency examines each Investigational New Drug (IND) Application individually and considers the IND in the context of the standards in the regulation.

The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section 505(i)(3) of the FD&C Act; 21 U.S.C. 355(i)(3)). FDA's implementing regulations in 21 CFR 312.42 identify the circumstances that may justify a clinical hold. In this section of this letter, we explain why, at this time, FDA has not granted Petitioner's request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

The grounds for placing a proposed or ongoing study, including an ongoing Phase 3 study, on clinical hold are provided in 21 CFR 312.42(b). Specifically, 21 CFR 312.42(b)(1)(i) through (b)(1)(v) provides grounds for imposition of a clinical hold of a Phase 1 study. Additionally, as stated in 21 CFR 312.42(b)(2), FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that: (i) any of the conditions in 21 CFR 312.42(b)(1)(i) through (b)(1)(v) apply; or (ii) the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. As indicated in more detail below, at this time, FDA has not granted Petitioner's request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

- 21 CFR 312.42(b)(1)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.

  FDA continues to evaluate all available information and, based on this evaluation thus far, does not believe that human subjects in any COVID-19 vaccine study that includes pediatric subjects are or would be exposed to an unreasonable and significant risk of illness or injury. The Agency reviews the protocols for COVID-19 vaccine clinical trials proposing to enroll pediatric subjects when they are submitted to the IND, in addition to any subsequent protocol amendments. For those clinical trials that have proceeded to studying COVID-19 vaccines in pediatric populations, FDA has determined that, based on all information currently available to FDA, the studies do not expose subjects to unreasonable risks.

- 21 CFR 312.42(b)(1)(ii): The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that clinical investigators named in the IND for any COVID-19 vaccine clinical trial including pediatric subjects are not qualified by reason of their scientific training and experience to conduct the investigation described in the INDs.

- 21 CFR 312.42(b)(1)(iii): The investigator brochure is misleading, erroneous, or materially incomplete.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the investigator brochures for any ongoing COVID-19 vaccine investigation which includes or proposes to include pediatric subjects are misleading, erroneous, or materially incomplete.

- 21 CFR 312.42(b)(1)(iv): The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the IND for any ongoing COVID-19 vaccine in which

pediatric subjects are enrolled contains insufficient information required under 21 CFR 312.23 to assess the risks to pediatric subjects participating in the studies.

- 21 CFR 312.42(b)(1)(v) [provides, in part, that]: The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring)….

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that any COVID-19 vaccine studies enrolling pediatric subjects are excluding from eligibility men or women – including male and female adolescents and teenagers - with reproductive potential.

- 21 CFR 312.42(b)(2)(ii): The plan or protocol for the Phase 2 or Phase 3 investigation is clearly deficient in design to meet its stated objectives.

  The Agency reviewed the protocols for the COVID-19 vaccine investigations involving pediatric subjects at the time they were submitted to the INDs, as well as any subsequent amendments as they were submitted, and has determined that the study designs meets their stated objectives.

  At this time, the Agency is aware of no information to indicate that the protocols for any ongoing clinical investigations of COVID-19 vaccines involving pediatric subjects are clearly deficient in design to meet their stated objectives.

FDA has reviewed the issues raised in the Petition relating to the request to "immediately refrain from allowing minors to participate in COVID vaccine trials." Petition at 1. For the reasons outlined above, and in light of information currently available to FDA, FDA has determined that grounds do not exist to grant Petitioner's request to place all COVID-19 vaccine clinical investigations involving pediatric subjects on clinical hold pursuant to 21 CFR 312.42.

2. Request that FDA Refrain from Issuing EUA Amendments for Authorized COVID-19 Vaccines to Include Indications for Pediatric Populations

The Petition requests, among other things, that "[g]iven the extremely low risk of COVID illness in children, FDA should . . . immediately refrain from amending EUAs to include children. . . ." Petition at 1. To the extent that the Petition requests that FDA refrain from issuing EUA amendments for any of the Authorized COVID-19 Vaccines to include an indication for use in pediatric populations, this section explains why FDA is not granting this request.

In determining whether to issue an EUA for a product, including an amendment to an EUA in order to include additional populations within the indication, the FDA evaluates the available evidence and assesses, among other things, any known or potential risks and any known or potential benefits. Once a manufacturer submits an EUA request for a COVID-19 vaccine, the FDA then evaluates the request and determines whether the relevant statutory criteria are met,

taking into account the totality of the scientific evidence about the vaccine that is available to the agency.

As noted in Section II.b. above, in the October 2020 Guidance, FDA provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[89] In this guidance, FDA explained that, in the case of such vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[90] FDA has also stated, in this guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[91]

a. Information Submitted by Petitioner Regarding the Safety of COVID-19 Vaccines in Pediatric Populations

Petitioner argues that, for children, the risks of COVID-19 vaccines outweigh the benefits because the risk of severe COVID in children is "extremely low." Petition at 1. Petitioner cites to several sources of information in support of this argument (Petition at 12-13), which FDA has reviewed and considered.

Petitioner cites to CDC data[92] regarding death rates of children in the United States due to COVID-19 and compares the number of children who have died involving COVID-19 to the number of Americans of all ages who have died of COVID-19. Petitioner's approach of simply comparing raw numbers of deaths involving COVID-19 in the U.S. pediatric population against the raw numbers of deaths involving COVID-19 in the overall U.S. population (all sexes and all ages), does not provide a sufficient scientific basis upon which to conclude, as Petitioner contends, that the "relative risk for children due to COVID is very low." Petition at 12. Additionally, as discussed in further detail below, based on available data and information, we have concluded that COVID-19 is a serious or life-threatening disease or condition in the 12-17 age group.

As a preliminary matter, we note that petitioner's claim that "the death rate following either vaccination in this age group, assuming these children were trial enrollees, is approximately 2 in 2,000 or 0.1%." (Petition at 13) is erroneous. Our review of the submitted clinical trial data associated with the Pfizer-BioNTech COVID-19 Vaccine has not identified any deaths among adolescent or young adult vaccinees.[93] Additionally, as described in a NEJM article regarding

[89] October 2020 Guidance at 6-7.
[90] Id. at 3.
[91] Id. at 4.
[92] CDC, National Center for Health Statistics, Weekly Updates by Select Demographic and Geographic Characteristics, https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge.
[93] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download (stating that there were two deaths in vaccine recipients, both >55 years of age). FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for

the Moderna COVID-19 vaccine, no deaths were reported among vaccine recipients enrolled in the clinical trial of Moderna COVID-19 Vaccine.[94] Investigational New Drug (IND) application sponsors are required to notify FDA in a written safety report of any adverse experience associated with the use of the drug that is both serious and unexpected.[95] Any death that occurs in a vaccine clinical trial therefore must be reported to FDA and is then thoroughly evaluated by FDA to determine the cause and whether or not the death is plausibly related to the vaccine.

Additionally, we note that Petitioner raised concerns regarding VAERS reports in arguing that COVID-19 vaccines should not be authorized for pediatric populations because, Petitioner argues, "[a]vailable evidence strongly suggests that the vaccine is much more dangerous to children than the disease." Petition at 12. VAERS data reviewed to date has not identified risks related to vaccination that would cause the Agency to change its view that the benefits of vaccination with the Pfizer-BioNTech COVID-19 vaccine outweigh the risks of vaccination in individuals 12-17 years of age. VAERS data is evaluated thoroughly, and as described in greater detail above, FDA acts on safety signals. VAERS reports, however, are not used *in isolation* to draw an association between a vaccine and a possible adverse event.

Finally, we note that petitioner cites to an opinion piece published in the British Medical Journal, which presents the authors' opinion that the benefits of COVD-19 vaccination are outweighed by its risks in pediatric populations.[96] FDA has reviewed this article and determined it does not present evidence that the EUA standard could not be met for pediatric populations. Indeed, as explained in the FDA Decision Memorandum for the Pfizer-BioNTech COVID-19 Vaccine EUA, based on FDA's review of all available data regarding the benefits and risks of the use of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age, we have determined that this EUA meets the statutory criteria for individuals in this age range.[97]

Petitioner has failed to present data demonstrating that, for children, the risks of COVID-19 vaccines outweigh their benefits because the risk of severe COVID in children is "extremely low." Petition at 1. As explained in this section, the information submitted by Petitioner does not support this contention. As explained in further detail below, data reviewed by the Agency demonstrates that the Pfizer-BioNTech COVID-19 Vaccine, which is authorized for use in individuals 12 years of age and older, continues to demonstrate that the known and potential benefits of this vaccine outweigh its known and potential risks in this population. Any other EUA requests for COVID-19 vaccine candidates for use in pediatric populations will be reviewed on a case-by-case basis under the applicable statutory standards. Therefore, we deny

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Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download (stating that there were no deaths among vaccine recipients 12-15 years of age during the follow-up period).

[94] K. Ali, et al., Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents, NEJM (Aug. 11, 2021), DOI: 10.1056/NEJMoa2109522, https://www.nejm.org/doi/10.1056/NEJMoa2109522.

[95] 21 CFR § 312.32(c)(1)(i).

[96] W. Pegden, V. Prasad, S. Baral, Covid vaccines for children should not get emergency use authorization, BMJ (May 7, 2021), https://blogs.bmj.com/bmj/2021/05/07/covid-vaccines-for-children-should-not-get-emergency-use-authorization/.

[97] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

Petitioner's request to refrain from amending any EUA for a COVID-19 vaccine to include a pediatric indication.

3. Request that FDA Immediately Revoke all EUAs for COVID-19 Vaccines with Pediatric Indications

Petitioner requests that FDA "immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines." Petition at 1. Currently, only the Pfizer-BioNTech COVID-19 vaccine is indicated for the prevention of COVID-19 in pediatric populations. This vaccine is indicated for individuals 12 years of age and older. As explained in section III.B.i.1.b above, in addressing this request, it is necessary to consider the EUA revocation standard provided in section 564(g)(2) of the FD&C Act. In this section, we assess whether any of these statutory conditions under which FDA may revoke an EUA are met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and explain why the EUA revocation standard is not met for this vaccine.

a. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines with Pediatric Indications

As explained above in section III.b.i.1.b of this letter, Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

> (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
> (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
> (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

As explained above in section II.b., the EUA Guidance notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[98]

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccine with Pediatric Indications

As explained in detail above in section III.b.i.1.b., section 564(b)(2) of the FD&C Act sets forth the statutory standard for termination of an EUA declaration. This provision provides that an EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary, in consultation with the Secretary of Defense, that the circumstances that precipitated the declaration have ceased or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is

[98] EUA Guidance at 28.

satisfied with respect to the Authorized COVID-19 Vaccine with a pediatric indication. Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUA for the Authorized COVID-19 vaccine with a pediatric indication under the authority in section 564(g)(2)(A) of the FD&C Act.

1. The Criteria for The Issuance of the Authorized COVID-19 Vaccine with Pediatric Indications Continues to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and why, therefore, FDA may not revoke this EUA under the authority in section 564(g)(2)(B) of the FD&C Act.

a. Serious or life-threatening disease or condition.

As explained above in section III.b.i.1 of this letter, section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, "the agent(s) referred to in [the HHS Secretary's EUA declaration] can cause a serious or life-threatening disease or condition." FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard. FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.[99] In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.[100] On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in FDA Decision Memoranda for the Authorized COVID-19 Vaccines.[101]

Since March 1, 2020, approximately 1.7 million COVID-19 cases in individuals 12 to 17 years of age have been reported to the Centers for Disease Control and Prevention (CDC). Among these cases approximately 11,700 resulted in hospitalization, with more than 691 ICU admissions

[99] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html.
[100] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.
[101] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

and more than 100 deaths. It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested. Children and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults. However, as with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock. As of June 28, 2021, the CDC received reports of 4196 cases and 37 deaths that met the definition for MIS-C.

Both FDA and CDC have convened advisory committee meetings to discuss the use of COVID-19 vaccines in pediatric populations. Overall, these advisory committees agreed that there is a serious risk of severe COVID-19 in the pediatric population. In particular, the June 23, 2021 ACIP meeting discussed the benefits and risks of the use of COVID-19 mRNA vaccines in adolescents and young adults.[102] This discussion raised the point that adolescents and young adults have the highest COVID-19 incidence rates, and that these populations are an increasing proportion of COVID-19 cases reported. COVID-19-associated deaths continue to occur in these populations; since April 2021, 316 deaths have been reported among persons aged 12-29 years. Additionally, post-COVID conditions -- such as Multisystem Inflammatory Syndrome in Children (MIS-C) and Multisystem Inflammatory Syndrome in Adults (MIS-A) -- can occur in these populations following COVID-19.

Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines with Pediatric Indications.

b. Evidence of Effectiveness

As explained above in section III.b.i.1.b of this letter, Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2." FDA has determined that based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition in the 12 through 17 years of age population.[103] The basis for this determination is explained in detail in FDA's decision memoranda regarding

[102] CDC, Megan Wallace and Sara Oliver, CDC ACIP Meeting Presentation, COVID-19 mRNA Vaccines in Adolescents and Young Adults: Benefit-Risk Discussion, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf; CDC, ACIP Meeting Slides, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html.
[103] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

the Pfizer BioNTech COVID-19 Vaccine EUA.[104] Section III.b.ii of this letter explains why Petitioner's arguments regarding the effectiveness of the Authorized COVID-19 Vaccines, and the information submitted by Petitioner in support of this argument, does not change FDA's analysis regarding the effectiveness of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age.

Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

c. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." Petitioner argues that the current risks of serious adverse events or deaths associated with the authorized COVID-19 vaccines outweigh the benefits of COVID-19 vaccines in the pediatric population. Section III.b.i.1.b.ii above addresses these arguments insofar as they apply to the Authorized COVID-19 Vaccines generally and explains why they are unavailing. Section III.b.ii above addresses Petitioner's arguments regarding the safety of COVID-19 vaccines in the pediatric population, and explains why the information submitted by Petitioner does not change FDA's analysis regarding the benefits and risks of the authorized COVID-19 vaccines in the pediatric population.

d. No Alternatives

Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]." To the extent Petitioner's contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 in pediatric populations (and that therefore the requirement in section 564(c)(3) of the FD&C Act is not met with respect to the Authorized COVID-19 Vaccine with a pediatric indication), this argument is erroneous.

As described above in section III.b.i.1.b, there are no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population, other than the newly-approved BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty). That vaccine is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.[105] The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect to cover those 12 through

[104] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

[105] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, https://www.fda.gov/media/146338/download.

15 years of age, the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and until sufficient approved vaccine can be manufactured and distributed for use in those 16 years of age and older. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Therefore, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19.

ii. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above in section III.b.i.1.b of this letter, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[106]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 through 17 years of age because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of this vaccine, when used to prevent COVID-19, outweigh the known and potential risks of this vaccine in individuals 12 through 17 years of age, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in this population.

As described in detail in section III.b.i.1 above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

[106] EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.[107]

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Pfizer-BioNTech COVID-19 Vaccine, to support a revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine in the 12-17 years of age population are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances. FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA. Accordingly, as noted above, we deny Petitioner's request that FDA "immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines." Petition at 1.

iii. Petitioner's Request that FDA Immediately Revoke Tacit Approval that Pregnant Women may Receive any EUA or Licensed COVID-19 Vaccines and Immediately Issue Public Guidance

Petitioner requests that FDA "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect." Petition at 1. Because "tacit approval," or revocation thereof, is not a concept that exists in applicable statutes or regulations governing FDA-regulated products, FDA interprets this as a request that the labeling for the Authorized COVID-19 Vaccines, and any COVID-19 vaccine that may be licensed in the future, contain a contraindication for use during pregnancy.
In addressing Petitioner's request for a contraindication, we first discuss the risks posed to pregnant women by COVID-19. We then provide an explanation of the regulatory framework for prescription drug labeling for approved and licensed products, including the standard for inclusion of contraindications in such labeling to inform health care providers of information such as known hazards in the use of a particular drug as well as the requirements for pregnancy and lactation information in such labeling. We then discuss labeling for products made available under an EUA and explain why a contraindication for use in pregnant women was not included in the labeling for the Authorized COVID-19 Vaccines. This section concludes with an explanation for why Petitioner's requests for a contraindication for use during pregnancy in the labeling for the Authorized COVID-19 Vaccines – and BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) - is denied.

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[107] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151611/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

1. COVID-19 in Pregnancy

As a preliminary matter, we note that COVID-19 poses significant risks to pregnant women. CDC explains that "observational data regarding COVID-19 during pregnancy demonstrate that pregnant people with COVID-19 have an increased risk of severe illness, including illness resulting in intensive care admission, mechanical ventilation, extracorporeal membrane oxygenation, or death, though the absolute risk for these outcomes is low. Additionally, they are at increased risk of preterm birth and might be at an increased risk of adverse pregnancy complications and outcomes, such as preeclampsia, coagulopathy, and stillbirth."[108]

2. Certain Content and Format Requirements for Prescription Drug Labeling for Products Approved Under NDAs or BLAs

As FDA explains in the draft guidance for industry, Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format, ("Pregnancy and Lactation Guidance") "[p]rescription drug labeling is a communication tool. Its principal objective is to make available to health care providers the detailed prescribing information necessary for the safe and effective use of a drug, in a manner that is clear and useful to providers when prescribing for and counseling patients."[109] In order to achieve this objective, prescription labeling must be based on scientific data, and it must not be inaccurate, false, or misleading.[110]

FDA regulations govern the content and format of prescription drug labeling for approved drugs and biological products (see, e.g., §§ 201.56 and 201.57 (21 CFR 201.57); see also 21 CFR 201.100(c)). The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[111] FDA regulations require that the labeling of most prescription drug products include Highlights of Prescribing Information, which are intended to summarize the information that is most important for prescribing the drug safely and effectively and to facilitate access to the more detailed information within product labeling (see § 201.57(a)). FDA regulations further require that the labeling for most prescription drugs include, among other information, the following sections: Contraindications; Warnings and Precautions; Adverse

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[108] CDC, Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States, Vaccination of Pregnant or Lactating People, https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fclinical-considerations.html#pregnant.

[109] Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry, Draft Guidance, July 2020, at 2, https://www.fda.gov/media/90160/download.

[110] 21 CFR § 201.56(a)(2) "The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."

[111] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (Physician Labeling Rule). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in § 201.57, see § 201.80 (21 CFR 201.80). The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.

Reactions; and Use in Specific Populations, which includes a subsection on Pregnancy (see § 201.57(c)(1), (5), (6), (7), and (9)(i)).

a. Contraindications

The Contraindications section must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.[112] This could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks do not outweigh any potential benefit of the drug to any patient.[113]

b. Pregnancy

The Pregnancy subsection is located under the Use in Specific Populations section (see § 201.57(c)(9)(i)). On December 4, 2014, FDA issued a final rule amending the regulations on the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule (PLLR)).[114] The PLLR revisions to the regulations were intended "to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that would be useful for decision making by health care providers and their patients."[115] The labeling content and format requirements in § 201.57(c)(9)(i), as revised by the PLLR, took effect on June 30, 2015, with a phased implementation schedule for drugs (including biological products) that are the subject of NDAs, BLAs, and efficacy supplements that had been approved on or after June 30, 2001.[116] The PLLR also requires for all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, that the Pregnancy subsection of labeling be revised to remove the pregnancy letter categories A, B, C, D, and X.[117]
Information in the Pregnancy subsection of labeling may present, in greater detail, a topic that is briefly summarized in another section of labeling (e.g., Warnings and Precautions).[118] FDA has explained that when a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail.[119]

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[112] See § 201.57(c)(5); see also FDA guidance for industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format; Guidance for Industry, October 2011 (Warnings Guidance), at 8, https://www.fda.gov/media/71866/download.
[113] See Warnings Guidance at 8.
[114] Final rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (PLLR) (79 FR 72064, December 4, 2014), https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for.
[115] Id. at 72066.
[116] See §§ 201.56(b) and 201.57(c)(9)(i).
[117] §§ 201.57(c)(9) and 201.80; see also 79 FR 72064 at 72095 (December 4, 2014).
[118] PLLR, 79 FR 72064 at 72085 (December 4, 2014).
[119] See FDA guidance for industry, Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements; Guidance for Industry, February 2013, https://www.fda.gov/media/71836/download.

Under current labeling requirements, information in the Pregnancy subsection of labeling is presented under the following subheadings: Pregnancy Exposure Registry; Risk Summary; Clinical Considerations; and Data.[120] The labeling for the Authorized COVID-19 Vaccines includes the Pregnancy Exposure Registry and the Risk Summary subheadings. We briefly describe these subheadings below.

i. Pregnancy Exposure Registry

If there is a scientifically acceptable pregnancy exposure registry for the drug, the labeling must state that fact and provide contact information needed for enrolling in or obtaining information about the registry.

ii. Risk Summary

The Risk Summary subheading is required under the Pregnancy subsection because certain statements must be included even when no product-specific data are available, given that all pregnancies have a background risk of birth defect, loss, or other adverse outcomes.[121] The Risk Summary must contain risk statement(s) that describe for the drug the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.[122] When multiple data sources are available, the risk statements are required to be presented in the following order: human, animal, and pharmacologic.[123]

When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s) and include its incidence and the effects of dose, duration of exposure, and gestational timing of exposure.[124] If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, the risk summary must contain a quantitative comparison of that risk to the risk for the same outcome in infants born to women who were not exposed to the drug, but who have the disease or condition for which the drug is indicated to be used.[125] When risk information is not available for women with the disease or condition(s) for which the drug is indicated, the risk summary must contain a comparison of the specific outcome in women exposed to the drug during pregnancy against the rate at which the outcome occurs in the general population.[126]

When animal data are available, the risk statement based on such data must describe the potential risk for adverse developmental outcomes in humans and summarize the available data.[127] This statement must include: the number and type(s) of species affected; timing of exposure; animal doses expressed in terms of human dose or exposure equivalents; and outcomes for pregnant animals and offspring.[128]

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[120] § 201.57(c)(9)(i).
[121] § 201.57(c)(9)(i)(B).
[122] Id.
[123] Id.
[124] § 201.57(c)(9)(i)(B)(1).
[125] Id.
[126] Id.
[127] § 201.57(c)(9)(i)(B)(2).
[128] Id.

With respect to pharmacology, when the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks.[129]

3. Inclusion of Contraindications and Pregnancy Information in the Labeling for the Authorized COVID-19 Vaccines

For the emergency use of an unapproved product, section 564(e)(1)(A)(i) of the FD&C Act requires that FDA must—to the extent practicable given the applicable circumstances of the emergency, and as FDA finds necessary and appropriate to protect the public health—establish appropriate conditions designed to ensure that health care professionals administering the authorized product are informed:

- That FDA has authorized the emergency use of the product (including the product name and an explanation of its intended use);
- Of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- Of available alternatives and their benefits and risks.

Therefore, as explained in the EUA Guidance, FDA recommends that "a request for an EUA include a 'Fact Sheet' for health care professionals or authorized dispensers that includes essential information about the product. In addition to the required information, Fact Sheets should include . . . any contraindications or warnings."[130] The EUA guidance also recommends that, for unapproved drugs that do not have "FDA-approved labeling for any indication . . . in addition to the brief summary information found in a Fact Sheet, the sponsor also develop more detailed information similar to what health care professionals are accustomed to finding in FDA-approved package inserts."[131]

The sponsors for all the Authorized COVID-19 Vaccines submitted such prescribing information in the EUA requests, and FDA reviewed and authorized this labeling. The Fact Sheets for Healthcare Providers Administering Vaccine for all of the Authorized COVID-19 Vaccines contain Contraindications and Warnings and Precautions sections because FDA determined that sufficient data existed for inclusion of such information in the authorized labeling for these vaccines.[132]

FDA did not, however, require inclusion of a contraindication for pregnancy in the authorized labeling. The authorized COVID-19 vaccines are authorized for use in an age range that includes women of childbearing age and are not contraindicated for use in pregnant women because FDA

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[129] § 201.57(c)(9)(i)(B)(3).
[130] EUA Guidance at 22.
[131] EUA Guidance at 23.
[132] Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, https://www.fda.gov/media/146304/download; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144413/download Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144637/download.

is not aware of any evidence that suggests the risk of use of the Authorized COVID-19 Vaccines in pregnant women would clearly outweigh any possible therapeutic benefit.[133] Nor has the Petitioner presented any such evidence in the Petition. Accordingly, this request is denied.

4. Inclusion of Contraindications and Pregnancy Information in the Labeling for Licensed COVID-19 Vaccines

With respect to Petitioner's request that FDA "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect" (Petition at 1; emphasis added), as explained above in this section, FDA regulations require the Contraindications section of the labeling for an approved drug or biological product to describe any situations in which the drug or biological product should not be used because the risk of use "clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.[134] The approved COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) is indicated for use in an age range that includes women of childbearing age and is not contraindicated for use in pregnant women because FDA is not aware of any evidence that suggests the risk of use of BioNTech's COVID-19 vaccine in pregnant women would clearly outweigh any possible therapeutic benefit,[135] nor has the Petitioner presented any such evidence in the Petition.

In its review of a BLA for any future COVID-19 vaccine candidate, FDA will apply the regulatory standards outlined above in determining, on a case-by-case basis, whether to include a contraindication in pregnancy, or any other contraindications, in the approved labeling for such a vaccine. Accordingly, Petitioner's request is denied.

iv. Petitioner's Request that FDA Immediately Amend its Guidance regarding Certain Approved Drugs [chloroquine drugs, ivermectin, "and any other drugs demonstrated to be safe and effective against COVID"]

Petitioner requests that the Agency "immediately amend its existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID, to comport with current scientific evidence of safety and efficacy at currently used doses and immediately issue notifications to all stakeholders of this change." Petition at 2. FDA has not issued "guidance for the use of chloroquine drugs, ivermectin, and other drugs

[133] FDA's decision memoranda for the Authorized COVID-19 Vaccines discuss FDA's analysis of all available data regarding the use of the Authorized COVID-19 Vaccines in pregnancy. *See*, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

[134] See § 201.57(c)(5); see also Warnings Guidance at 8.

[135] See FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

demonstrated to be safe and effective against COVID."[136] FDA has, however, analyzed adverse event information and made publicly available safety issues regarding the use of hydroxychloroquine and chloroquine to treat patients with COVID-19.[137] FDA has also informed the public that it has received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses, that taking large doses of ivermectin can cause serious harm, that ivermectin is not authorized or approved by FDA to treat COVID-19, and that using any treatment for COVID-19 that is not approved or authorized by the FDA, unless part of a clinical trial, can cause serious harm.[138] You have not provided any evidence to suggest that the safety information in these communications is inaccurate. Thus, to the extent you are requesting that FDA withdraw or revise these previous safety communications, that request is denied.

v. Petitioner's Request that FDA Issue Guidance to the Secretary of Defense and the President

Petitioner requests that FDA "issue guidance to the Secretary of the Defense and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers under 10 U.S.C. § 1107(f) or 10 U.S.C. § 1107a." Petition at 2.

FDA denies this request because FDA, an agency within the U.S. Department of Health and Human Services, does not issue guidance of the type requested to the President of the United States or to other Departments in the executive branch of the U.S. federal government.

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[136] Under FDA's good guidance practices regulations, a "guidance document" is defined as "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue." 21 CFR 10.115(a)(b)(1). The regulation provides further that "[g]uidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies." Importantly, the provision at 21 CFR 10.115(b)(3), excludes from the definition of "guidance document" general information documents provided to consumers or health professionals, such as those communications that have been provided to the public regarding the use of hydroxychloroquine, chloroquine, and ivermectin to treat patients with COVID-19. 21 CFR 10.115(b)(3) states: "[g]uidance documents do not include: Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms." (Emphasis added.)

[137] FDA Drug Safety Communication, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, April 24, 2020, updated June 15, 2020 and July 1, 2020, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or; FDA, CDER Office of Surveillance and Epidemiology Pharmacovigilance Memorandum, May 19, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/OSE%20Review_Hydroxychloroquine-Cholorquine%20-%2019May2020_Redacted.pdf.

[138] FDA Consumer Update, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19, March 5, 2021, https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19; FDA Letter to Stakeholders, Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans, April 10, 2020, https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans.

vi. Petitioner's Request that FDA Issue Guidance to Stakeholders Regarding the Option to Refuse or Accept Administration of Investigational COVID-19 Vaccines

Petitioner requests that FDA "issue guidance to all stakeholders in digital and written formats to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences, under 21 U.S.C. § 360bbb-3(e)(1)(a)(ii)(III) 1 and the informed consent requirements of the Nuremberg Code."[139] We interpret this request to relate to the Authorized COVID-19 Vaccines and third parties' decisions with respect to unvaccinated individuals' participation in certain activities. Such decisions by third parties with respect to employment, education, and other non-FDA-regulated activities would not be within FDA's purview. Accordingly, FDA denies Petitioner's request.

vii. Petitioner's Request that FDA Issue Guidance Regarding Marketing and Promotion of COVID-19 Vaccines

FDA notes that your Petition discusses statements made by CDC. For requests intended for CDC, you should contact CDC directly.

As explained above in section III.b.i.1.b of this response, the EUA revocation standard in section 564(g)(2) of the FD&C Act is not met for any of the Authorized COVID-19 Vaccines. With respect to Petitioner's request to issue guidance pending revocation of the EUAs for the Authorized COVID-19 Vaccines, we note that the EUA Guidance contains a section regarding advertising for EUA products. As explained in the EUA guidance, FDA may, under section 564(e)(1)(B) of the FD&C Act, on a case-by-case basis and to the extent feasible given the circumstances of a particular public health emergency, establish certain additional conditions that FDA finds to be necessary or appropriate to protect the public health.[140] The EUA guidance explains that, under section 564(e)(4) of the FD&C Act, FDA may place conditions on "advertisements and other promotional descriptive printed matter (e.g., press releases issued by the EUA sponsor) relating to the use of an EUA product, such as requirements applicable to prescription drugs under section 502(n) . . . ."[141] FDA's authority under section 564(e)(4) ordinarily does not extend to statements by third parties who have no direct connection with the EUA sponsor.

For the Authorized COVID-19 Vaccines, FDA has determined that such conditions are necessary to protect the public health. Accordingly, the Letter of Authorization for each of the Authorized COVID-19 Vaccines contains conditions related to printed matter, advertising, and promotion.[142] Given the current public health emergency, FDA does not see a need to expend the resources

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[139] Concerns about potential State vaccine requirements are better directed to the States. FDA does not mandate use of vaccines.
[140] EUA Guidance at 26.
[141] Id. at 27.
[142] FDA, Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), https://www.fda.gov/media/150386/download; FDA, Moderna COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), https://www.fda.gov/media/144636/download; FDA, Janssen COVID-19 Vaccine Letter of Authorization (June 10, 2021), https://www.fda.gov/media/146303/download.

necessary to develop and issue additional guidance on this topic. Thus, because FDA has already issued guidance addressing advertising and promotion of EUA products, and because FDA has established conditions related to printed matter, advertising, and promotion for all of the Authorized COVID-19 Vaccines, FDA denies Petitioner's request to issue additional guidance on this issue.

c. Conclusion

FDA has considered Petitioner's requests as they relate to the Authorized COVID-19 Vaccines and the approved COVID-19 Vaccine. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petition. Therefore, we deny the Petition in its entirety.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

Vaccines are both biological products under the Public Health Service Act (PHS Act) (42 U.S.C. § 262) and drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 321). The PHS Act defines a "biological product" as including a "vaccine…or analogous product…applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). The FD&C Act defines drug to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. § 321(g)(1)(B).

Under the PHS Act, a biological product may not be introduced or delivered for introduction into interstate commerce unless a biologics license is in effect for the product. 42 U.S.C. § 262(a)(1)(A).

B. Clinical Investigations of Vaccines

Before a vaccine is licensed (approved) by FDA and can be used by the public, FDA requires that it undergo a rigorous and extensive development program that includes laboratory research, animal studies, and human clinical studies to determine the vaccine's safety and effectiveness.

The PHS Act and the FD&C Act provide FDA with the authority to promulgate regulations that provide a pathway for the study of unapproved new drugs and biologics. 42 U.S.C. § 262(a)(2)(A) and 21 U.S.C. § 355(i). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND), which describes the protocol, and, among other things, assures the safety and rights of human subjects. These regulations are set out at 21 CFR Part 312. See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

The regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, Phase 1 studies typically enroll fewer than 100 participants and are designed to look for very common side effects and preliminary evidence of an immune response to the candidate vaccine. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects, such as redness and swelling at the injection site or fever, and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies are usually of sufficient size to detect less common adverse events.

If product development is successful and the clinical data are supportive of the proposed indication, the completion of all three phases of clinical development can be followed by submission of a Biologics License Application (BLA) pursuant to the PHS Act (42 U.S.C. § 262(a)), as specified in 21 CFR § 601.2.

C. Biologics License Applications

A BLA must include data demonstrating that the product is safe, pure, and potent and that the facility in which the product is manufactured "meets standards designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). FDA does not consider an application to be filed until FDA determines that all pertinent information and data have been received. 21 CFR § 601.2. FDA's filing of an application indicates that the application is complete and ready for review but is not an approval of the application.

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[143] and clinical information necessary to make a benefit-risk assessment, and to determine whether "the establishment(s) and the product meet the applicable requirements established in [FDA's regulations]." 21 CFR § 601.4(a).

FDA generally conducts a pre-license inspection of the proposed manufacturing facility, during which production of the vaccine is examined in detail. 42 U.S.C. § 262(c). In addition, FDA carefully reviews information on the manufacturing process of new vaccines, including the results of testing performed on individual vaccine lots.

FDA scientists and physicians evaluate all the information contained in a BLA, including the safety and effectiveness data and the manufacturing information, to determine whether the application meets the statutory and regulatory requirements. FDA may also convene a meeting of its advisory committee to seek input from outside, independent, technical experts from various scientific and public health disciplines that provide input on scientific data and its public health significance.

As part of FDA's evaluation of a vaccine as a whole, FDA takes all of a vaccine's ingredients into account (including preservatives and adjuvants). FDA licenses a vaccine only after the Agency has determined that the vaccine is safe and effective for its intended use, in that its benefits outweigh its potential risks.

[143] Also referred to as Pharmaceutical Quality/CMC.

Exhibit 4

Vaccines and Related Biological Products Advisory Committee Meeting
October 26, 2021

FDA Briefing Document

EUA amendment request for Pfizer-BioNTech COVID-19 Vaccine for use in children 5 through 11 years of age

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1 EXECUTIVE SUMMARY

On October 6, 2021, Pfizer submitted a request to FDA to amend its Emergency Use Authorization (EUA) to expand use of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for prevention of COVID-19 caused by SARS-CoV-2 in individuals 5 through 11 years of age (hereafter 5-11 years of age). The proposed dosing regimen is a 2-dose primary series, 10 µg mRNA/per dose, administered 3 weeks apart. This EUA request initially included safety data from 1,518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age who are enrolled in the Phase 2/3 portion (Cohort 1) of an ongoing randomized, double-blinded, placebo-controlled clinical trial, C4591007. Among Cohort 1 participants, 95.1% had safety follow-up ≥2 months after Dose 2 at the time of the September 6, 2021 data cutoff for this cohort. Safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients enrolled in the Phase 2/3 portion (Cohort 2) of the trial were provided later during FDA's review of the EUA amendment request to allow for more robust assessment of serious adverse events and other adverse events of interest (e.g., myocarditis, pericarditis, anaphylaxis). The median duration of follow-up in Cohort 2 was 2.4 weeks post Dose 2 at the time of the October 8, 2021 data cutoff for this cohort. Vaccine effectiveness was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay). Neutralizing antibody titers at 1 month post-Dose 2 in children 5-11 years of age were compared to neutralizing antibody titers 1 month post-Dose 2 among a subset of study participants 16-25 years of age randomly selected from efficacy study C4591001 who had previously received two doses of 30 µg BNT162b2. A supplemental descriptive analyses of vaccine efficacy (VE) among Cohort 1 participants (following accrual of 19 total confirmed COVID-19 cases) was also provided during FDA's review of the EUA amendment request.

The immunogenicity analyses evaluated neutralizing antibody titers against the USA_WA1/2020 reference strain, as assessed by microneutralization assay, among study participants with no evidence of prior SARS-CoV-2 infection up to 1 month post-Dose 2. Immunobridging endpoints and statistical success criteria were as follows:

- SARS-CoV-2 neutralizing antibody GMTs measured at 1 month after Dose 2 in study C4591007 Phase 2/3 Cohort 1 participants 5-11 years of age vs. GMTs at 1 month after Dose 2 in a randomly selected subset of study C4591001 Phase 2/3 participants 16-25 years of age, with immunobridging success criteria of >0.67 for the lower bound of the 95% confidence interval around the GMT ratio (5-11 years of age / 16-25 years of age), and a point estimate of the GMT ratio ≥1.0.

- Percentage of participants with seroresponse (≥4-fold rise from baseline [pre-Dose 1]), with immunobridging success criterion of >-10% for the lower bound of the 95% confidence interval around the difference (5-11 years of age minus 16-25 years of age) in seroresponse rates.

Immunobridging statistical success criteria, as described above, were met. Subgroup analyses of immunogenicity by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on an exploratory 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo) with no evidence of SARS-CoV-2 infection up to 1 month post-Dose 2.

In the supplemental descriptive efficacy analysis, VE against symptomatic COVID-19 after 7 days post Dose 2 up to October 8, 2021 (data cutoff) was 90.7% (2-sided 95% CI: 67.4%, 98.3%) in participants 5-11 years of age without evidence of prior SARS-CoV-2 infection. Totals of 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group, most of which occurred during July-August 2021 when the Delta variant was prevalent in the United States. At the time of the data cutoff, none of these cases met the criteria for severe COVID-19.

Solicited local and systemic adverse reactions (ARs) reported among Cohort 1 participants generally occurred more frequently after Dose 2, with the most commonly reported solicited ARs being pain at the injection site (71%), fatigue (39.4%), and headache (28%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and most resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1 BNT162b2 recipients was lymphadenopathy (n=13; 0.9%). More BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) than placebo recipients (n=4; 0.53%). Overall, from the combined safety database of 3,109 BNT162b2 recipients (Cohorts 1 and 2), 4 participants reported serious adverse events; all were considered by the study investigator and FDA as unrelated to vaccination. There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions.

FDA conducted a quantitative benefit-risk analysis to evaluate predicted numbers of symptomatic COVID-19 cases, hospitalizations, ICU admissions, and deaths that would be prevented per million fully vaccinated children 5-11 years of age over a 6-month period, as compared with predicted numbers of vaccine-associated excess myocarditis cases, hospitalizations, ICU admissions and deaths per million fully vaccinated children 5-11 years of age. The model conservatively assumed that the risk of myocarditis/pericarditis associated with the 10 µg dose in children 5-11 years of age would the same as the estimated risk associated with the 30 µg dose in adolescents 12-15 years of age from Optum healthcare claims data. While benefits of vaccination were highly dependent on COVID-19 incidence, the overall analysis predicted that the numbers of clinically significant COVID-19-related outcomes prevented would clearly outweigh the numbers of vaccine-associated excess myocarditis cases over a range of assumptions for COVID-19 incidence. At the lowest evaluated COVID-19 incidence (corresponding to the June 2021 nadir), the predicted number of vaccine-associated myocarditis cases was greater than the predicted number of COVID-19 hospitalizations prevented for males and for both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks under this low incidence scenario. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

This October 26, 2021 VRPBAC meeting is being held to discuss whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age.

2 SARS-COV-2 VIRUS AND COVID-19 DISEASE

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death. Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported.[1,2] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[3] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.[4,5] However, COVID-19 associated hospitalizations and deaths have occurred in children (see below), and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.[6]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 15, 2021, has caused approximately 239 million cases of COVID-19, including 4.8 million deaths worldwide.[7] In the United States, more than 44 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 722,000 deaths. [8,9] Of the total COVID-19 cases reported in the United States to date, 22.3% occurred among individuals <18 years of age, with 8.7% occurring among 5-11-year-olds.[10] Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021; however, beginning in late June 2021 a rise in cases was observed, including in children, associated with the highly transmissible Delta variant that is now predominant in the United States.[11] As of the week ending October 2, 2021, the Delta variant comprised greater than 99% of tested strains in the United States.[12] During the last week in August 2021, new COVID-19 infections in individuals less than 18 years of age surpassed those in adults 18 to 64 years of age for the first time during the pandemic.[13] In the United States, COVID-19 cases occurring in children 5-11 years now constitute 39% of cases in individuals younger than 18 years of age.[14] Among cases of COVID-19 in individuals less than 18 years of age from the COVID-NET network[a], approximately 4,300 have resulted in hospitalization.[15] As of October 17, 2021, 691 deaths from COVID-19 have been reported in the United States in individuals less than 18 years of age, with 146 deaths in the 5-11 year age group.[16]

The most common underlying medical conditions among hospitalized children were chronic lung disease (29%), obesity (25%) and neurologic disorders (23%). A total of 68% of hospitalized children had more than one underlying condition. Obesity and feeding tube dependence were associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, metabolic

[a] COVID-NET covers approximately 10% of the U.S. population; The current network covers nearly 100 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and four additional states through the Influenza Hospitalization Surveillance Project (IA, MI, OH, and UT); see https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html.

conditions, or with congenital heart disease.[17] As in the adult population, COVID-19 in children disproportionally affects underrepresented racial and ethnic groups, with hospitalizations and deaths more frequent among Native American/Alaskan, Hispanic or Latin American, and non-Hispanic Black children than among White children.[18,19]

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis.[20,21] While the overall incidence of myocarditis following COVID-19 infection is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. The risk is lowest among individuals 25-39 years and higher in persons less than 16 years and older than 50 years of age.[22] Myocarditis may also present as part of the Multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection.[23] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least 2 affected organs. In severe cases, hypotension and shock can occur. Most patients have laboratory markers indicating damage to the heart.[24] During the pandemic, a rise in MIS-C cases has generally lagged behind a rise observed in COVID-19 infections by several weeks,[25] with one study demonstrating the peak in MIS-C cases occurring 31 days following the peak in laboratory-confirmed COVID-19 cases.[26] Between May 2020 and October 4, 2021, the CDC received reports of 5,217 cases and 46 deaths that met the definition for MIS-C; the median age of participants was 9 years with half of the cases occurring in children ages 5 to 13 years. Males comprised 60% of cases, and 61% were reported in children who were reported as Hispanic or Black.[27] Up to 66.7% of patients with MIS-C had cardiac involvement, [28] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[29] One study of outcomes in children with MIS-C followed up to 9 months found that while 76% children with MIS-C required ICU admission and therapy with inotropes or pressors; most symptoms, including cardiovascular manifestations, resolved within 1 to 4 weeks.[30] Limited data are available on long-term outcomes in MIS-C.

While children and adolescents appear less susceptible to SARS-CoV-2 infection and generally have a milder COVID-19 disease course as compared with adults,[31,32] adolescents and adults have similar SARS-CoV-2 viral loads in their nasopharynx, so adolescents may play a role in community transmission.[33,34] Transmission of SARS-CoV-2 virus from children can occur in both household and school settings.[35,36] In schools, transmission depends on the transmission rates locally, variants circulating in the community, vaccination rates, and other preventive mitigation strategies. Transmission between school staff members may be more common than transmission involving students.[37] There is evidence that SARS-CoV-2 transmission is greater in secondary and high schools than elementary schools.[38,39] Outbreaks of COVID-19 have been reported in settings where children congregate, such as summer youth camps.[40,41]

In addition to morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education). Other impacts of COVID-19 on children include limited access to basic services such as healthcare and child protective services, and social isolation due to disruption of school, sports, and social group gatherings. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the

United States, the longer-term effect of the Delta variant and the potential role of other variants on the future course of the pandemic is uncertain.

3 AUTHORIZED AND APPROVED VACCINES AND THERAPIES FOR COVID-19

FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below. The Pfizer-BioNTech COVID-19 Vaccine is also FDA approved for use as a 2-dose primary series in individuals 16 years of age and older, under the trade name COMIRNATY (see Section 4).

Table 1. Emergency Use Authorizations of COVID-19 Vaccines

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Pfizer-BioNTech	2-dose primary series (3 weeks apart)	Individuals ≥16 years of age Individuals ≥12 years of age	December 11, 2020 May 10, 2021
Pfizer-BioNTech	3rd primary series dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Pfizer-BioNTech	Booster dose (at least 6 months after completing a primary series of COMIRNATY and/or Pfizer-BioNTech COVID-19 Vaccine)	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	September 22, 2021
Moderna	2-dose series (4 weeks apart)	2-dose primary series in adults ≥18 years of age	December 18, 2020
Moderna	3rd dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Moderna	Booster dose (at least 6 months after completing a primary series of Moderna COVID-19 Vaccine	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	October 20, 2021
Janssen	Single dose	Individuals ≥18 years of age	February 27, 2021
Janssen	Booster dose	Individuals ≥18 years of age	October 20, 2021
Pfizer, Moderna and Janssen	Single heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19	Same population(s) as those eligible to receive a booster dose of the vaccine used for primary vaccination	October 20, 2021

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
	vaccine (same interval as authorized for a booster dose of the vaccine used for primary vaccination)		

Remdesivir is the only product currently approved by the FDA for treatment of COVID-19 requiring hospitalization, and its approved use is limited to individuals 12 years of age and older. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies		
• Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued September 16, 2021 May 26, 2021 Reissued September 9, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a] Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs		
• Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg
Immune Modulators		
• Baricitinib • Actemra	Reissued July 29, 2021 June 24, 2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

a Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
b Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

4 COMIRNATY (COVID-19 VACCINE, mRNA)

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.). COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two doses (0.3 mL each) 3 weeks apart, with each dose containing 30 µg mRNA. COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19. COMIRNATY is also authorized under EUA for use as a 2-dose primary series in individuals 12 years of age and older, for use as a third primary series dose in individuals 12 years of age and older with certain immunocompromising conditions, and for use as a single booster dose administered at least 6 months after completion of a primary series to individuals 65 years of age and older, individuals 18 through 64 years of age at increased risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The vaccine authorized under EUA is also known as the Pfizer-BioNTech COVID-19 Vaccine. During clinical development, the vaccine was called BNT162b2.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately and is stored at 20°C to 25°C. The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contains six doses of 0.3 mL of vaccine. COMIRNATY does not contain preservative.

4.1 Efficacy of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

Efficacy of BNT162b2 for the prevention of COVID-19 occurring at least 7 days after completion of a 2-dose primary series was evaluated in an ongoing Phase 3 study, C4591001, in approximately 44,000 participants randomized 1:1 to receive two doses of either BNT162b2 or placebo, 3 weeks apart. Participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age). The population for the vaccine efficacy analysis that supported approval of COMIRNATY included participants 16 years of age and older who had been enrolled from July 27, 2020, and who were followed for the development of COVID-19 during blinded placebo-controlled follow-up through as late as March 13, 2021. Overall, 60.8% of participants in the BNT162b2 group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after the primary series in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in subjects without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in subjects with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

4.2 Safety of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

In study C4591001, the most commonly reported solicited adverse reactions (occurring in ≥10% of participants) among BNT162b2 vaccine recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain

(45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported solicited adverse reactions in BNT162b2 vaccine recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

Among participants 16 through 55 years of age, SAEs from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 0.8% of BNT162b2 recipients and 0.9% placebo recipients. In a similar analysis, in participants 56 years of age and older serious adverse events (SAEs) were reported by 1.8% of BNT162b2 recipients and 1.7% of placebo recipients who received at least 1 dose of BNT162b2 or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after the primary series. There were no notable patterns between treatment groups for specific categories of SAEs (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the BNT162b2 group and 17 in the placebo group. None of the deaths were considered related to vaccination.

4.3 Effectiveness and safety of a 2-dose primary series of Pfizer-BioNTech COVID-19 Vaccine in adolescents 12-15 years of age

On May 10, 2021, FDA authorized the use of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age based on safety and effectiveness data from an ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 2,260 participants 12-15 years of age.

Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race and sex. In the supplemental efficacy analysis, VE after 7 days post Dose 2 was 100% (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0% (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provided compelling direct evidence of clinical benefit in addition to the immunobridging data.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of greater than 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%),

muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local and systemic adverse reactions occurred in up to 2.4% of 12-15-year-old BNT162b2 recipients, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. No deaths were observed in this age group during the follow-up period. SAEs, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious AEs among study participants 12-15 years of age that would suggest a causal relationship to BNT162b2 vaccine.

4.4 Cases of myocarditis/pericarditis reported in BNT162b2 recipients in ongoing clinical trials of BNT162b2

Two cases of myocarditis have been reported in BNT162b2 recipients in study C4591001:

- A male participant ≥55 years of age, with no medical history, reported myocarditis 28 days after Dose 2 of BNT162b2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff.
- A male participant who was randomized to blinded placebo group at age 15 years and subsequently unblinded and crossed over to open label BNT162b2 at age 16 years was diagnosed with myopericarditis beginning 2 days after Dose 2 of BNT162b2. He was hospitalized on Day 3 and treated with IVIG, non-steroidal anti-inflammatory medications and steroids, and discharged the following day. He was followed by a cardiologist and seen for follow-up 2 months after vaccination. At that time the cardiologist recommended limited activity. The investigator concluded that the there was a reasonable possibility that the myopericarditis was related to vaccine administration due to the plausible temporal relationship. FDA agrees with this assessment.

4.5 Post-EUA and post-licensure surveillance

As of October 21, 2021, more than 240 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. (CDC COVID Data Tracker, accessed on October 22, 2021). Among all COVID-19 vaccines, 205,046 individuals less than 12 years of age have received at least one dose and 125,656 are fully vaccinated (CDC COVID Data Tracker, accessed on October 22, 2021).

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the Pfizer-BioNTech COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of October 18, 2021, VAERS received 442,763 reports (including 270,342 U.S. reports), of which 854 U.S. reports were in children 5-11 years of age, 9,523 U.S. reports were in children

12-15 years of age, and 5,821 U.S. reports were in adolescents 16-17 years of age. The top ten most frequently reported MedDRA preferred terms (PTs) included:

- Overall most frequent PTs: headache, fatigue, pyrexia, SARS-CoV-2 test, dizziness, pain, nausea, chills, pain in extremity, dyspnoea
- Most frequent PTs in in persons ≤17 years of age: dizziness, syncope, headache, pyrexia, nausea, product administered to patient of inappropriate age, chest pain, fatigue, vomiting, loss of consciousness.

Note that a report may have one or more PTs. An additional query of VAERS for U.S. reports by dose number retrieved the following: 127,747 reports after Dose 1; 100,730 reports after Dose 2; and 5,223 reports after dose 3 (data as of October 18, 2021).

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets. Review of passive surveillance AE reports and the Sponsor's periodic safety reports does not indicate any new safety concerns, including in adolescents. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern.

Anaphylaxis

Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[42][43] Anaphylaxis is an important identified risk in the pharmacovigilance plan (PVP) and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The estimated crude reporting rate for anaphylaxis in the U.S. is 6.1 cases per million doses at this time based on the above VAERS data.

Myocarditis and pericarditis

Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis, particularly within 7 days following administration of the second dose of the 2-dose primary series. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12 through 17 years of age (~71.5 cases per million second primary series doses among males age 16-17 years and 42.6 cases per million second primary series doses among males age 12-15 years as per CDC presentation to the ACIP on August 30, 2021). In an FDA analysis of the Optum healthcare claims database, the estimated excess risk of myocarditis/pericarditis approached 200 cases per million fully vaccinated males 16-17 years of age and 180 cases per million fully vaccinated males 12-15 years of age.[44] Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Myocarditis and pericarditis were added as important identified risks in the PVP and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The Sponsor is conducting additional post-authorization/post-marketing

studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

5 EUA AMENDMENT REQUEST FOR THE PFIZER-BIONTECH COVID-19 VACCINE FOR USE IN CHILDREN 5-11 YEARS OF AGE

On October 6, 2021, Pfizer and BioNTech submitted a request to amend this EUA to include use of a 2-dose primary series of the Pfizer-BioNTech COVID-19 Vaccine (10 µg each dose, administered 3 weeks apart) in individuals 5-11 years of age for active immunization to prevent COVID-19 caused by severe acute coronavirus 2 (SARS-CoV-2).

The request is accompanied by safety data from 1,518 BNT162b2 and 750 placebo (saline) Phase 2/3 participants 5-11 years of age in ongoing clinical study, C4591007, of which a total of 1,444 (95.1%) had safety follow-up ≥2 months after Dose 2 at the time of a September 6, 2021 data cutoff, and data from an additional 1,591 BNT162b2 and 788 placebo participants with a median duration of follow-up of 2.4 weeks post-Dose 2 at the time of an October 8, 2021 data cutoff. Vaccine effectiveness in children 5-11 years of age was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, as assessed by SARS-CoV-2 mNG microneutralization assay) among C4591007 study participants 5-11 years of age following completion of a primary series to antibody titers of those of young adults 16-25 years of age who received two doses of 30 µg BNT162b2 in study C4591001. Efficacy against COVID-19 disease was assessed descriptively in study C4591007 participants 5-11 years of age.

Vaccine formulation

Authorization is being requested for a modified formulation of the Pfizer-BioNTech COVID-19 Vaccine. Each dose of this formulation contains 10 µg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 that is formulated in lipid particles and supplied as a frozen suspension in multiple dose vials.

To provide a vaccine with an improved stability profile, the Pfizer-BioNTech COVID-19 Vaccine for use in children 5-11 years of age uses tromethamine (Tris) buffer instead of the phosphate-buffered saline (PBS) as used in the previous formulation and excludes sodium chloride and potassium chloride. The packaged vials for the new formulation are stored frozen at -90°C to -60°C. The frozen vials may be thawed and stored at refrigerator at 2°C to 8°C for up to 10 weeks.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex. For the 10-µg RNA dose, each 1.3-mL filled via vial must be diluted with 1.3mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume. After dilution, the vials should be stored at 2°C to 25°C and should be used within 12 hours.

6 EUA REQUIREMENTS, GUIDANCE AND CONSIDERATIONS PERTAINING TO COVID-19 VACCINES

6.1 U.S. requirements to support issuance of an EUA for a biological product

Based on the declaration by the Secretary of the U.S. Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens

living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

6.2 FDA guidance for industry related to COVID-19 vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" February 2021, originally issued October 2020).[45] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in children 5-11 years of age. The timing, design, and appropriate endpoints for pediatric studies are discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent COVID-19" from June 2020.[46]

6.3 Regulatory considerations for clinical development of COVID-19 vaccines in children

The Vaccines and Related Biological Products Advisory Committee convened on June 21, 2021 to discuss, in general, the data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

Effectiveness

Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to a young adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease. Based on

available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric mean titer [GMT] and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric vs. young adult populations.

Safety

The size of the safety database sufficient to assess risks of COVID-19 vaccines for EUA in pediatric age groups would generally be the same as for other preventive vaccines for infectious diseases, provided that no specific safety concern is identified that could reasonably be evaluated in pre-authorization clinical trials. These safety data would include characterization of common adverse reactions (reactogenicity, including injection site and systemic adverse reactions), and less common but medically important adverse reactions. Depending on prior experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure and have at least 6 months of follow-up evaluations after completion of the vaccination regimen. Since COVID-19 vaccines represent a new class of vaccines, with many of the lead candidates based on new platform technologies, an appropriate overall pediatric safety database would approach the upper end of this range, with adequate representation across all pediatric age groups, in particular younger age groups (e.g., <12 years) that are less physiologically similar to adults. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well-controlled studies to support licensure. If another COVID-19 vaccine is licensed or authorized for use in the age group(s) enrolled in the trial, recommended by public health authorities, and widely available such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control.

Within the overall pre-licensure safety database, solicited reactogenicity could be adequately characterized among several hundred trial participants in each relevant age group. Additionally, safety evaluation in all trial participants would include collection of all AEs through at least 1 month after each study vaccination and collection of serious and other medically attended AEs for the duration of the trial. Although longer-term follow-up (through 1 year or longer post-vaccination) of trial participants would be important to ongoing assessment of both benefits and risks, completion of such longer-term follow-up would not be a prerequisite to licensure unless warranted by a specific safety concern. Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials.

7 FDA REVIEW OF CLINICAL SAFETY AND EFFECTIVENESS DATA

7.1 Overview of study C45910007

The EUA amendment request contains safety, immunogenicity, and descriptive efficacy data from children 5-11 years of age enrolled in C4591007, an ongoing Phase 1/2/3, randomized, placebo-controlled study. The comparator group for the immunobridging analyses to support vaccine effectiveness in this age group was a random subset of Phase 2/3 participants 16-25 years of age enrolled in study C4591001, the study in which vaccine efficacy against COVID-19 was established in individuals 16 years of age or older.

Data from study C4591007

- Phase 2/3: a total of 3,109 BNT162b2 (10 µg) recipients and 1528 placebo recipients 5-11 years of age

  – Cohort 1: 1,518 BNT162b2 (10 µg) recipients and 750 placebo recipients, of whom 1,444 (95.1%) and 714 (95.2%), respectively, had at least 2 months of safety follow-up after completing a 2-dose primary series (data cutoff September 6, 2021). Summary tables for solicited adverse reactions (ARs) and immunogenicity analyses are based on this cohort of subjects. A descriptive efficacy analysis was also based on this cohort; at the time of this Briefing Document was prepared, FDA has not fully verified the underlying data or Pfizer-BioNTech's conclusions from this analysis.

  – Cohort 2: A second cohort of 1,591 BNT162b2 (10 µg) recipients and 778 placebo recipients had a median duration of follow-up of 2.4 weeks post-Dose 2 at the time of data cutoff (October 8, 2021). Safety data from this cohort were provided for further assessment of SAEs and AEs of clinical interest. Data verification is in process, but not yet finished at the time this briefing book was completed.

- Phase 1 data to support dosage selection for Phase 2/3 portion of the study

Table 3. Study C4591007*: Participants 5-11 Years of Age (10 µg BNT162b2)

Study Number/ Countries	Description	BNT162b2 N	Placebo (Saline) N	Study Status
C4591007 United States, Finland, Poland, and Spain	Phase 1/2/3 randomized, placebo-controlled; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 16 Phase 2/3: 3,109	Phase 1:0 Phase 2/3: 1,528	Ongoing

N=Number of randomized participants as of data cutoff dates July 16, 2021 (all Phase 1 participants), September 6, 2021 (Phase 2/3 Cohort 1: 1,518 BNT162b2, 750 placebo; includes participants starting March 24, 2021) and October 8, 2021 (Phase 2/3 cohort 2: 1,591 BNT162b2, 788 placebo; first subject in this second cohort randomized August 15, 2021).
*First participant, first visit was March 24, 2021.

7.2 Study design

Study C4591007 is an ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled safety, immunogenicity, and efficacy study. This section presents the design for the Phase 2/3 portion of the study in children 5-11 years of age. Please see Appendix 1 for Phase 1 study design.

Phase 2/3 is being conducted in the United States, Finland, Poland, and Spain. The Phase 2/3 portion of the study did not exclude children with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, children with known HIV, hepatitis B or hepatitis C, or stable pre-existing disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment).

Participants were randomized 2:1 to receive two doses of 10 µg BNT162b2 or placebo (saline), 3 weeks apart. Participants who turned 12 years of age during the study would have the opportunity to receive the EUA-authorized dose level of 30 µg (12-15 years of age) if they originally received placebo.

Immunogenicity evaluation

Immunobridging was based on SARS-CoV-2 neutralizing antibody responses in study C4591007 Phase 2/3 (Cohort 1) participants 5-11 years of age compared to neutralizing antibody responses in a random subset of study C4591001 participants 16-25 years of age, as measured by 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) against the reference strain (USA_WA1/2020) at 1 month after a primary series. The primary analysis is based on the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2.

Primary endpoints and statistical success criteria

- Immunobridging success based on GMT was declared if the lower limit (LL) of the 95% CI for the GMT ratio (5-11 years of age / 16-25 years of age) was >0.67, and the point estimate of the GMT ratio was ≥1.0.
- Immunobridging success based on the seroresponse rate was declared if the LL of the 95% CI for the difference in seroresponse rates (5-11 years of age minus 16-25 years of age) was >-10%. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination (pre-Dose 1) to 1 month after Dose 2.

Efficacy evaluation

A secondary objective is to evaluate efficacy of BNT162b2 against laboratory-confirmed symptomatic COVID-19 occurring from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection and in participants with or without evidence of prior SARS-CoV-2 infection. A descriptive analysis was conducted once 19 confirmed cases had accrued.

Safety evaluation

Reactogenicity (solicited local and systemic adverse reactions)

The participants' parents or participants themselves recorded reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain).

Unsolicited adverse events

Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after Dose 2, and SAEs from Day 1 to 6 months after Dose 2, or the data cutoff date (Phase 1: of July 16, 2021; Phase 2/3: September 6, 2021). AEs were categorized by frequency and maximum severity according to system organ class (SOC) and preferred term (PT), according to MedDRA, and relationship to the study intervention was assessed. Deaths are recorded to the end of the study.

Adverse events of clinical interest

The occurrence of certain AEs including lymphadenopathy and myocarditis/pericarditis were assessed as part of the safety review, as well as additional AEs requested by FDA (including anaphylaxis, Bell's palsy, appendicitis, pregnancy exposures and outcomes, and MIS-C cases).

Analysis populations

Pertaining to participants 5-11 years of age

- Safety: All participants who receive at least 1 dose of the study intervention.

- All-available immunogenicity: All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
- Evaluable immunogenicity: All eligible randomized participants who receive two doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
- Evaluable efficacy: All randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.

Data analysis cutoff dates:

- All Phase 1 participants: July 16, 2021
- Phase 2/3 Cohort 1: September 6, 2021; includes participants starting March 24, 2021
- Phase 2/3 Cohort 2: October 8, 2021; first subject in this cohort was randomized August 15, 2021

7.3 Disposition of Phase 2/3 participants

Cohort 1

Cohort 1 was comprised 1,528 BNT162b2 10 µg participants and 757 placebo participants; 11 (0.7%) BNT162b2 and 6 (0.8%) placebo participants did not receive any study agent. Two BNT162b2 participants (0.1%) and two placebo participants (0.3%) discontinued vaccination before the 1 month post-Dose 2 follow-up; none resulted from an AE. Three participants turned 12 years of age during the course of the study and became eligible to receive 30 µg BNT162b2 under EUA; two of these participants received two doses of 10 µg BNT162b2 prior to being unblinded, and the other participant received both doses of placebo before being unblinded and withdrew to receive a COVID-19 vaccine outside of the study; data from these participants were included in endpoint analyses up to the point at which they were unblinded.

Safety population: solicited ARs, unsolicited AEs, SAEs and AEs of clinical interest were assessed in a total of 2,268 (1,518 10 µg BNT162b2, 750 placebo) participants 5-11 years of age; 95% of participants in each study group completed at least 2 months of safety follow-up after Dose 2. Five BNT162b2 recipients and six placebo recipients withdrew from the study, mainly due to voluntary withdrawal.

Comparator group for immunogenicity: The comparator group for immunobridging analyses consisted of 300 evaluable participants 16-25 years of age who received both doses of BNT162b2 30 µg and were randomly selected from study C4591001 Phase 2/3.

Table 4. Disposition of Immunogenicity Populations, Phase 2/3, Participants 5-11 Years of Age (Study C4591007 Cohort 1) and Participants 16-25 Years of Age (Study C4591001)

Disposition	5-11 years of age BNT162b2 (10 µg) n (%)	5-11 years of age Placebo n (%)	16-25 years of age BNT162b2 (30 µg) n (%)
Randomized to receive BNT162b2[a]	322 (100.0)	163 (100.0)	300 (100.0)
All-available immunogenicity population	311 (96.6)	156 (95.7)	286 (95.3)
Excluded because they did not have at least 1 valid and determinate immunogenicity result after vaccination	11 (3.4)	7 (4.3)	13 (4.3)
Evaluable immunogenicity population	294 (91.3)	147 (90.2)	273 (91.0)
Without evidence of infection up to 1 month after Dose 2[b]	264 (82.0)	130 (79.8)	253 (84.3)
Subjects excluded from evaluable immunogenicity population	28 (8.7)	16 (9.8)	27 (9.0)
Reason for exclusion (subjects may have been excluded for >1 reason)			
Did not receive 2 doses of the vaccine as randomized	3 (0.9)	1 (0.6)	0
Did not receive Dose 2 within 19 to 42 days after Dose 1	3 (0.9)	2 (1.2)	3 (1.0)
Did not have at least 1 valid and determinate immunogenicity result within 28 to 42 days after Dose 2	13 (4.0)	14 (8.6)	21 (7.0)
Did not have blood draw at 1 month after Dose 2 visit	7 (2.2)	6 (3.7)	8 (2.7)
1 Month after Dose 2 blood draw outside of window (28-42 days after Dose 2)	6 (1.9)	8 (4.9)	13 (4.3)
Had important protocol deviation(s) as determined by the clinician	10 (3.1)	0	4 (1.3)

%:n/N. n = number of participants with the specified characteristic. N = number of randomized participants in the specified group; this value is the denominator for the percentage calculations.

a. Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding ant body [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

b. Participants may have been excluded for more than 1 reason.

Cohort 2

In the Phase 2/3 safety expansion, 1,598 participants were randomized to receive BNT162b2 and 796 were randomized to placebo. At the time of the October 8, 2021 cutoff, most participants (98.7%) had received both Dose 1 and Dose 2. Seven participants in the BNT162b2 group did not receive vaccine, for a Safety Population of 1,591. One participant in the BNT162b2 group discontinued from the vaccination period due to AEs of pyrexia and neutropenia that worsened from baseline (see Section 7.6.7, AEs leading to withdrawal). Two participants (0.1%) in the BNT162b2 group withdrew from the study before the 1 month period. Neither withdrawal was due to an AE.

Comorbidities at baseline

Comorbidities were defined as described in Kim et al. MMWR 2020.[47] Participants with any comorbidity, including obesity, constituted 20.6% of the BNT162b2 group and 20.3% of placebo group. The most common comorbidities at baseline in the Cohort 1 BNT162b2 group were obesity (11.5%), asthma (7.8%), neurologic disorders (1.3%), and congenital heart disease

(1.0%). Other comorbidities included diabetes in 2 participants (0.2%), and one participant each (0.1%) for acute lymphocytic leukemia (immunocompromising conditions), cystic fibrosis, and sickle cell disease.

Demographic characteristics were similar in Cohort 2 as Cohort 1. Overall, 11.1% of participants were obese. Comorbidities including obesity were found in 19.9% of participants. As in Cohort 1, the most common comorbidities were asthma, neurologic disorders and congenital heart disease.

7.4 Demographic and baseline characteristics

Demographic characteristics for the safety population of participants who received BNT162b2 10 µg in Phase 2/3 study C4591007 Cohort 1 are summarized in Table 5 below. Participants were predominately White, with a mean age of approximately 8 years. Of the BNT162b2 recipients, 11.5% met the definition of obesity, 8.8% had evidence of prior SARS-CoV-2 infection and 20.6% had comorbidities placing them at increased risk of severe COVID-19. More than 70% of participants were enrolled in the United States.

Table 5. Demographic and Baseline Characteristics, Phase 2/3, Participants 5-11 Years, Safety Population, Study C4591007 Cohort 1

Characteristic	C4591007 BNT162b2 10 µg (N[a]=1518) n[b] (%)	C4591007 Placebo (N[a]=750) n[b] (%)
Sex: Male	799 (52.6)	383 (51.1)
Sex: Female	719 (47.4)	367 (48.9)
Race: White	1204 (79.3)	586 (78.1)
Race: Black or African American	89 (5.9)	58 (7.7)
Race: American Indian or Alaska Native	12 (0.8)	3 (0.4)
Race: Asian	90 (5.9)	47 (6.3)
Race: Multiracial	109 (7.2)	49 (6.5)
Race: Not reported	9 (0.6)	7 (0.9)
Ethnicity: Hispanic or Latino	319 (21.0)	159 (21.2)
Ethnicity: Not Hispanic or Latino	1196 (78.8)	591 (78.8)
Age: Mean years (SD)	8.2 (1.93)	8.1 (1.97)
Age: Median (years)	8.0	8.0
Obese[c]: Yes	174 (11.5)	92 (12.3)
Obese[c]: No	1343 (88.5)	658 (87.7)
Baseline Evidence of Prior SARS-CoV-2 Infection: Negative[e]	1385 (91.2)	685 (91.3)
Baseline Evidence of Prior SARS-CoV-2 Infection: Positive[f]	133 (8.8)	65 (8.7)
Comorbidities[d]: Yes	312 (20.6)	152 (20.3)
Comorbidities[d]: No	1206 (79.4)	598 (79.7)
Country: Finland	158 (10.4)	81 (10.8)
Country: Poland	125 (8.2)	60 (8.0)
Country: Spain	162 (10.7)	78 (10.4)
Country: United States	1073 (70.7)	531 (70.8)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Demographic and baseline characteristic categories with 0 participants in any treatment group are not shown to avoid inadvertent unblinding through public disclosure.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
e. Negative N-binding antibody result and negative NAAT result at Visit 1 and no medical history of COVID-19.
f. Positive N-binding antibody result at Visit 1, positive NAAT result at Visit 1, or medical history of COVID-19.

Demographic characteristics in Cohort 2 were similar to Cohort 1.

Comparator group for immunogenicity: The 300 participants ages 16-25 years from study C4591001 were from sites in the United States (64%), Argentina (18%), Brazil (12%), and South Africa/Turkey/Germany (6% combined total).

Less than 0.8% of participants in either group received non-COVID-19 vaccines during the study; most were routine pediatric immunizations including diphtheria, pertussis, tetanus, human papillomavirus vaccine, and meningococcal vaccine.

7.5 Immunogenicity results

7.5.1 Primary immunogenicity objective

Immunogenicity of BNT162b2 was assessed based on analyses of GMTs and seroresponse rates for neutralizing antibody titers to the reference strain (USA_WA1/2020).

GMTs of neutralizing antibody titers to the reference strain

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of SARS-CoV-2 50% neutralizing GMT in children 5-11 years (10 µg each dose) compared to individuals 16-25 years (30 µg each dose) was 1.04. (95% CI: 0.93, 1.18). The lower bound of the 2-sided 95%CI for GMR was >0.67 and the point estimate was ≥1, which met FDA's requested criteria; see Table 6, below.

Table 6. SARS-CoV-2 Neutralizing GMTs (NT50)[a] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[b]

GMT (95% CI) 5-11 Years of Age Study C4591007 N[c] = 264	GMT (95% CI) 16-25 Years of Age Study C4591001 N[c] = 253	GMT Ratio (95% CI) (5-11 Years of Age / 16-25 Years of Age)[d]
1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer.
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
c. N = Number of Phase 2/3 participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window.
d. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the GMT ratio is greater than 0.67 and the point estimate of the GMT ratio is ≥1.0.

Rates of neutralizing antibody seroresponse to the reference strain

Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 are displayed in Table 7 below. Children 5-11 years of age had similar seroresponse (as measured from before vaccination to 1 month after Dose 2) rate as individuals 16-25 years of age. The difference between the two age groups was 0.0% (95% CI: -2.0%, 2.2%). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which was greater than the prespecified margin of -10% and thus immunobridging based on seroresponse rate was met, see Table 7 below.

Table 7. Seroresponse Rates[a,b] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age[b] Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[c]

Seroresponse 5-11 Years of Age Study C4591007 %[d] (95% CI) N= 264	Seroresponse 16-25 Years of Age Study C4591001 %[d] (95% CI) N= 253	% Difference in Seroresponse Rate (Age Group 5-11 Years minus Age Group 16-25 Years)[e] (95% CI)
99.2 (97.3, 99.9)	99.2 (97.2, 99.9)	0 (-2.0, 2.2)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay-NT50, reference strain: recombinant USA_WA1/2020.
b. Seroresponse defined as at least 4-fold rise relative to pre-Dose 1; if the baseline measurement was below LLOQ, a postvaccination titer of ≥4 × LLOQ was considered a seroresponse.
c. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
d. %: n/N. n = number of participants with seroresponse for the given assay at the given dose/sampling time point. N = Number of subjects with valid and determinate assay results for the specified assay within the specified window for blood samples collected at baseline (pre-Dose 1) and 1 month after primary series.
e. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Subgroup Analyses of Geometric Mean Titers

GMTs of SARS-CoV-2 neutralizing titers and seroresponse rates at 1 month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to evaluate by protocol-specified methods. Specifically, no notable differences in GMTs or seroresponse rates were observed by age (i.e., 5-6 year-old vs. 7-8 year-old vs. 9-11 year-old), sex, race, ethnicity, obesity (Y/N), or SARS-CoV-2 status.

In descriptive post hoc analyses of immunogenicity data based on the presence or absence of comorbidities (defined as described in Kim et al. MMWR 2020[47]), GMT and seroresponse rates among those with comorbidities were comparable to those without comorbidities.

7.5.2 Exploratory immunogenicity analyses against the Delta Variant

In response to FDA's request for immunogenicity data to support effectiveness of a 10 µg BNT162b2 primary series against the Delta variant, Pfizer submitted exploratory descriptive analyses of data from a randomly selected subset of participants (34 BNT162b2 recipients, 4 placebo recipients) with no evidence of infection up to 1 month post-Dose 2. These data were generated using non-validated SARS-CoV-2 plaque reduction neutralization assays with the

reference strain (USA-WA1/2020) and the Delta variant; the relative sensitivity of the two assays is not known.

Table 8. SARS-CoV-2 Neutralizing GMTs[a] at Pre-Dose 1 and 1 Month Post-Primary Series in C4591007 Phase 2/3 Cohort 1 Participants 5-11 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Primary Series, Evaluable Immunogenicity Population[b]

Assay Target	Time Point	BNT162b2 10 µg N=34 GMT (95% CI)	Placebo N=4 GMT (95% CI)
Reference strain	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	365.3 (279.0, 478.4)	10.0 (10.0, 10.0)
Delta variant	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	294.0 (214.6, 405.3)	10.0 (10.0, 10.0)

a. SARS-CoV-2 plaque reduction neutralization assay, SARS-CoV-2 strains: recombinant USA_WA1/2020 (reference), B.1.617.2 (Delta).
b. N = number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point. Participants with no serological or virological evidence of SARS-CoV-2 infection: defined as N-binding ant body [serum] negative from pre-Dose 1 to 1 month post-Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] prior to Dose 1 and Dose 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 1-month post-Dose 2, and no medical history of COVID-19.

7.5.3 Efficacy evaluation

Pfizer submitted supplemental, descriptive efficacy data for Phase 2/3 Cohort 1 participants 5-11 years of age, based on a total of 19 confirmed symptomatic COVID-19 cases occurring at least 7 days post-Dose 2, accrued up to the data cutoff of October 8, 2021. The evaluable efficacy population included 1,450 participants randomized to BNT162b2 and 736 participants randomized to placebo.

In participants 5-11 years of age without evidence of SARS-CoV-2 infection prior to Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.7% (95% CI: 67.4%, 98.3%), with 3 COVID-19 cases in the BNT162b2 group compared to 16 in the placebo group (2:1 randomization BNT162b2 to placebo). All cases of COVID-19 occurred in children without prior history of infection. None of these cases met the criteria for severe infection. Most of the cases occurred in July-August 2021. Comorbidities at baseline (including obesity) were present in total of 20.1% of cases. No virus sequence analyses were available to determine whether these cases were caused by the Delta variant or another variant.

7.6 Safety results

Please see the Appendix for Phase 1 study results.

Overview of adverse events: Phase 2/3

In C4591007 Phase 2/3 Cohort 1, e-diary data were collected on 1,511 participants for reactogenicity (local and systemic reactions). Overall, injection site reactions occurring within 7 days of vaccination with BNT162b2 were common, occurring in approximately 75% of participants after either Dose 1 or Dose 2. Systemic AEs occurred in approximately 50% of BNT162b2 recipients.

No participants withdrew because of AEs, and there were no deaths reported. SAEs occurred in one participant each from the BNT162b2 and placebo groups, and neither were considered by the investigator or FDA to be related to the investigational agent. Immediate unsolicited AEswere rare in this study, occurring in 0.3% or less after either Dose 1 or Dose 2. See Table 9 below.

Table 9. Safety Overview, Phase 2/3 Cohorts 1 and 2, Participants 5-11 Years, Safety Population, Study C4591007

Event	BNT162b2 10 µg n/N (%)	Placebo n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination		
Dose #1	3/1518 (0.2)	3/750 (0.4)
Dose #2	4/1515 (0.3)	2/746 (0.3)
Solicited injection site reaction within 7 days		
Dose #1	1150/1511 (76.1)	254/749 (33.9)
Dose #2	1096/1501 (73.0)	237/741 (32.0)
Solicited systemic AR within 7 days		
Dose #1	715/1511 (47.3)	334/749 (44.6)
Dose #2	771/1501 (51.4)	272/741 (36.7)
From Dose 1 through 1 month after Dose 2		
Any AE	166/1518 (10.9)	69/750 (9.2)
Unsolicited non-serious AE	166/1518 (10.9)	68/750 (9.1)
SAE	0/1518 (<0.1)	1/750 (0.1)
From Dose 1 through cutoff date[a] or participant unblinding[b]		
Withdrawal due to AEs	1/3109 (<0.1)	0/1538 (0.0)
SAE	4/3109 (0.1)	1/1538 (0.1)
Deaths	0/3109 (0.0)	0/1538 (0.0)

Note: MedDRA (v24.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
%:n/N. n = Number of participants with the specified characteristic. N = number of administered participants in the specified group; this value is the denominator for the percentage calculations.
a. Sept 13, 2021 for 1,518 BNT162b2 and 750 placebo; Oct 8, 2021 for the additional 1,591 BNT162b2 and 788 placebo.
b. Three participants (2 BNT162b2, 1 placebo) turned 12 years of age during the course of the study and elig ble to received 30 µg BNT162b2 under EUA; for this reason, the participants were unblinded to their treatment assignment.

7.6.1 Immediate AEs

Among the 1,518 Cohort 1 participants who received BNT162b2 Dose 1, a total of 3 reported any immediate AE, and all were injection site pain. Following Dose 2, 4 participants experienced an immediate AE, including 1 with nausea, 1 with injection site pain, 1 with injection site erythema, and 1 with erythema (skin and subcutaneous disorder).

7.6.2 Solicited adverse reactions

Solicited local adverse reactions generally occurred more commonly after Dose 2 and included pain at the injection site (71%), redness (18.5%) and swelling (15.3%). Systemic adverse reactions also occurred more frequently after Dose 2 and included fatigue (39.4%), headache (28%), and muscle pain (11.7%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset. Adverse reactions in BNT162b2 recipients that were graded as severe included 4 local reactions (3 participants with redness, 1 participant with swelling) and 1 systemic reaction (1 participant with muscle pain).

Rates of local and systemic adverse reactions in children 5-11 years of age were generally similar to those in individuals 12 years of age or older enrolled in study C4591001, with pain at the injection site slightly lower in the 5-11 year-old group, but redness and swelling slightly higher. Systemic adverse reactions such as fever, fatigue, headache, chills, and muscle pain were generally reported less frequently and were milder in severity in the 5-11 year-old group compared to individuals 12 years of age or older.

The frequencies of local and systemic adverse reactions within 7 days after each vaccination in participants with evaluable e-diary data are summarized in Tables 10, 11, and 12 below.

Table 10. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population[a], Study C4591007

Event	BNT162b2 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
Pain at the injection site[b]				
Any[d]	74.1	31.3	71.0	29.5
Mild	58.9	27.3	52.8	25.9
Moderate	14.9	4.0	17.8	3.5
Severe	0.3	0.0	0.3	0.0
Redness[c]				
Any[d]	14.7	5.7	18.5	5.4
Mild	9.5	4.9	9.5	4.2
Moderate	5.2	0.8	8.8	1.2
Severe	0.0	0.0	0.2	0.0
Swelling[c]				
Any[d]	10.5	2.7	15.3	2.7
Mild	5.6	1.7	7.8	2.0
Moderate	4.8	0.9	7.5	0.7
Severe	0.1	0.0	0.0	0.0

%:n/N. n=number of participants in the specified age group with the specified reaction. N=number of participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All participants in the specified age group who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[c] Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
[d] Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Table 11. Frequency of Solicited Systemic Reactions Within 7 Days After Dose 2 by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population, Study C4501007

Event	BNT162b2 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
Fever				
≥38.0°C	2.5	1.3	6.5	1.2
≥38.0°C to 38.4°C	1.5	0.5	3.4	0.7
>38.4°C to 38.9°C	0.8	0.7	2.5	0.4
>38.9°C to 40.0°C	0.2	0.1	0.5	0.1
>40.0°C	0.0	0.0	0.1	0.0
Fatigue[b]				
Any[e]	33.6	31.3	39.4	24.3
Mild	22.0	20.1	21.4	13.0
Moderate	11.3	11.1	17.3	11.2
Severe	0.3	0.1	0.7	0.1

Event	BNT162b2 Dose 1 N=1,511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1,501 %	Placebo Dose 2 N=741 %
Headache[b]				
Any[e]	22.4	24.1	28.0	18.6
Mild	16.5	17.5	18.7	12.6
Moderate	5.8	6.0	9.1	6.1
Severe	0.1	0.5	0.2	0.0
Chills[b]				
Any[e]	4.6	4.7	9.8	4.3
Mild	3.6	4.0	7.0	3.2
Moderate	1.1	0.7	2.7	0.9
Severe	0.0	0.0	0.1	0.1
Vomiting[c]				
Any[e]	2.2	1.5	1.9	0.8
Mild	1.7	1.5	1.8	0.8
Moderate	0.5	0.0	0.1	0.0
Severe	0.0	0.0	0.0	0.0
Diarrhea[d]				
Any[e]	5.9	4.1	5.3	4.7
Mild	5.2	4.1	4.8	4.3
Moderate	0.7	0.0	0.5	0.4
Severe	0.0	0.0	0.0	0.0
New or worsened muscle pain[b]				
Any[e]	9.1	6.8	11.7	7.4
Mild	6.4	4.7	7.7	5.1
Moderate	2.6	2.1	3.9	2.3
Severe	0.1	0.0	0.1	0.0
New or worsened joint pain[b]				
Any[e]	3.3	5.5	5.2	3.6
Mild	2.3	4.1	3.8	2.7
Moderate	1.1	1.3	1.4	0.9
Severe	0.0	0.0	0.0	0.0
Use of antipyretic or pain medication[f]	14.4	8.3	19.7	8.1

%: n/N. n = Number of participants with the specified reaction. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All participants in the specified age group who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
[c] Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
[d] Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
[e] Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f Severity was not collected for use of antipyretic or pain medication.

Table 12. Characteristics of Solicited Local and Systemic Adverse Reactions, Phase 2/3 Cohort 1, Participants 5-11 Years, Safety Population, Vaccine Group as Administered, Study C4591007

Event	BNT162b2 10 µg Dose 1 n[a]/N[b]	Placebo Dose 1 n[a]/N[b]	BNT162b2 10 µg Dose 2 n[a]/N[b]	Placebo Dose 2 n[a]/N[b]
Any solicited local reaction				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.0 (1, 12)
Persisted beyond 7 days	11/1511	9/749	8/1501	5/741

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
Redness				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 5)	2.0 (1, 6)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 8)	2.0 (1, 10)	1.0 (1, 11)
Persisted beyond 7 days	4/1511	1/749	2/1501	1/741
Swelling				
Day of onset: median (min, max)	2.0 (1, 4)	1.0 (1, 7)	2.0 (1, 4)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 9)	2.0 (1, 10)	1.0 (1, 12)
Persisted beyond 7 days	1/1511	1/749	2/1501	2/741
Pain at injection site				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.5 (1, 12)
Persisted beyond 7 days	7/1511	8/748	6/1501	5/740
Any solicited systemic reaction				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 10)
Persisted beyond 7 days	29/1511	15/749	30/1501	13/741
Fever				
Day of onset: median (min, max)	2.0 (2, 7)	2.5 (1, 7)	2.0 (1, 7)	6.0 (2, 7)
Duration: median (min, max)	1.0 (1, 3)	1.0 (1, 3)	1.0 (1, 5)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Fatigue				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 21)	2.0 (1, 9)	1.0 (1, 14)	1.0 (1, 10)
Persisted beyond 7 days	16/1511	7/748	17/1501	6/740
Headache				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 9)
Persisted beyond 7 days	12/1511	9/748	10/1501	6/740
Chills				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 7)	1.0 (1, 8)	1.0 (1, 8)
Persisted beyond 7 days	3/1511	0	1/1501	1/740
Vomiting				
Day of onset: median (min, max)	4.0 (1, 7)	4.0 (1, 6)	2.0 (1, 6)	3.0 (2, 6)
Duration: median (min, max)	1.0 (1, 5)	1.0 (1, 1)	1.0 (1, 2)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Diarrhea				
Day of onset: median (min, max)	3.0 (1, 7)	3.0 (1, 7)	3.0 (1, 7)	4.0 (1, 7)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 6)	1.0 (1, 28)	1.0 (1, 9)
Persisted beyond 7 days	1/1511	0	2/1501	2/740
New or worsened joint pain				
Day of onset: median (min, max)	2.0 (1, 6)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 7)	1.0 (1, 4)	1.0 (1, 18)	1.0 (1, 6)
Persisted beyond 7 days	0	0	1/1501	0

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
New or worsened muscle pain				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 9)	1.0 (1, 8)	1.0 (1, 9)	1.0 (1, 6)
Persisted beyond 7 days	1/1511	1/748	3/1501	0

a. n = Number of participants with the specified reaction persisted beyond 7 days.
b. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

7.6.3 Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing BNT162b2 and placebo groups by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the study groups, although certain subgroups such as Black or African American race and Hispanic/Latino ethnicity had too few participants to draw meaningful conclusions.

7.6.4 Unsolicited adverse events

Information about unsolicited AEs was collected from Dose 1 to 1 month post-Dose 2. No unsolicited AEs were reported by ≥1% of participants.

In Cohort 1, the most common unsolicited AE was lymphadenopathy, which was reported in 13 (0.9%) participants in the BNT162b2 group, and 1 participant in the placebo group (0.1%). Additional unsolicited AEs reported more commonly in the BNT162b2 group than in the placebo group included otitis externa in 7 participants (0.5%), arthropod bite, nasal congestion, oropharyngeal pain, and rash in 5 participants (0.3%), each. In BNT162b2 recipients, the following AEs were considered Grade 3 in severity: 1 tic, 1 rash (bilateral pleomorphic light eruption on arms). No Grade 4 (life-threatening AEs) were observed in the study. In Cohort 2, lymphadenopathy was reported in 6 (0.4%) vaccine recipients and 3 placebo recipients (0.4%).

7.6.5 SAEs

In Cohort 1, SAEs occurred at frequency of 0.1% in both BNT162b2 and placebo recipients. For BNT162b2 recipients, only one SAE was reported, an upper limb fracture. In Cohort 2, 3 BNT162b2 recipients (0.2%) reported a SAE: 1 infection of the knee, 1 foreign body ingestion, and 1 epiphyseal fracture. All SAEs reported in the study were considered by the study investigator to be unrelated to vaccination. FDA agrees with this assessment.

Deaths: No deaths have occurred during the study in either Cohort 1 or 2.

7.6.6 AEs of clinical interest

FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs among recipients 5-11 years of age in study C4591007 Phase 2/3 Cohort 1 through the September 6, 2021 cutoff date. SMQs (narrow and broad in scope) were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischaemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system (CNS) vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as

chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

For Cohort 1, the SMQ analyses resulted in identification of 19 participants with AEs of interest in the SMQs (narrow and broad in scope) in the BNT162b2 group and 6 in the placebo group. The SMQ analyses revealed an imbalance of AEs potentially representing allergic reactions, with 14 participants in the vaccine group (0.92%) reporting hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) compared with 4 participants in the placebo group (0.53%). See Table 13, below.

As in Cohort 1, SMQ analyses in Cohort 2 showed an imbalance of AEs in the BNT162b2 group compared to the placebo with respect to hypersensitivity, with 9 participants in the vaccine group (0.57%) and 4 in the placebo group (0.51%) reporting unsolicited AEs in this category, primarily skin and subcutaneous disorders of rash and dermatitis. Angioedema was reported in 3 (0.19%) in the vaccine group compared to 1 (0.13%) in the placebo group. These events included one participant with both angioedema and urticaria, and 3 participants with urticaria.

One participant, a 6-year-old female in the BNT162b2 group, had a non-serious AE of Henoch-Schonlein purpura which was diagnosed 21 days after Dose 1 and was considered non-serious.

No new or unexpected adverse reactions were identified based on these SMQ results.

Table 13. Standard MedDRA Query of Adverse Events by System Organ Class and Preferred Terms, Phase 2/3, Participants 5-11 Years, Safety Population, Vaccine Group as Administered, Cohort 1, Study C4591007

SMQ	Overall SMQ System Organ Class Preferred Term	BNT162b2 10 µg (N[a]=1,518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
Any	Participants with any unsolicited AEs within SMQ	19 (1.25)	6 (0.80)
Angioedema (SMQ)	Any unsolicited AEs within Angioedema (SMQ)	4 (0.26)	3 (0.40)
	Eye disorders	0	1 (0.13)
	Periorbital oedema	0	1 (0.13)
	General disorders and administration site conditions	1 (0.07)	0
	Swelling face	1 (0.07)	0
	Skin and subcutaneous tissue disorders	3 (0.20)	3 (0.40)
	Urticaria	3 (0.20)	3 (0.40)
Arthritis (SMQ)	Any unsolicited AEs within Arthritis (SMQ)	1 (0.07)	0
	Musculoskeletal and connective tissue disorders	1 (0.07)	0
	Synovitis	1 (0.07)	0
Convulsions (SMQ)	Any unsolicited AEs within Convulsions (SMQ)	0	0
Demyelination (SMQ)	Any unsolicited AEs within Demyelination (SMQ)	0	0
Hypersensitivity (SMQ)	Any unsolicited AEs within Hypersensitivity (SMQ)	14 (0.92)	4 (0.53)
	Eye disorders	1 (0.07)	1 (0.13)
	Conjunctivitis allergic	1 (0.07)	1 (0.13)
	General disorders and administration site conditions	1 (0.07)	0
	Injection site rash	1 (0.07)	0
	Immune system disorders	0	1 (0.13)
	Hypersensitivity	0	1 (0.13)
	Skin and subcutaneous tissue disorders	12 (0.79)	2 (0.27)
	Dermatitis	1 (0.07)	0

SMQ	Overall SMQ System Organ Class Preferred Term	BNT162b2 10 µg (N[a]=1,518) n[b] (%)	Placebo (N[a]=750) n[b] (%)
	Dermatitis allergic	1 (0.07)	0
	Dermatitis contact	3 (0.20)	0
	Eczema	1 (0.07)	1 (0.13)
	Rash	5 (0.33)	0
	Rash erythematous	0	1 (0.13)
	Rash macular	1 (0.07)	0
	Rash pruritic	1 (0.07)	0
Peripheral neuropathy (SMQ)	Any unsolicited AEs within Peripheral neuropathy (SMQ)	0	0
Vasculitis (SMQ)	Any unsolicited AEs within Vasculitis (SMQ)	0	0

Note: MedDRA (v24.0) coding dictionary applied.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants reporting at least 1 occurrence of the specified event category. For "any unsolicited AEs within SMQ," n = the number of participants reporting at least 1 occurrence of any unsolicited AEs within SMQ.

In Cohorts 1 and 2, “chest pain” was reported in a total of 12 participants: 6 assigned to the BNT162b2 group and 6 assigned to placebo. Chest pain resolved in all participants within 1-2 days of onset. No participants required a cardiac evaluation or ER visit, and none were hospitalized. In each case the AE was considered to be noncardiac in origin.

7.6.7 AEs leading to study withdrawal

In C4591007 Phase 2/3 Cohort 1, there were no AEs leading to withdrawal. In Cohort 2 with a follow-up cutoff of October 8, 2021, 1 participant was withdrawn due to AEs of fever 2 days after Dose 1 and worsening of neutropenia (previously diagnosed as benign transient neutropenia. Dose 2 was not administered.

7.7 Study C4591007 Phase 2/3 summary

This EUA request included safety data from 1,518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age in the Phase 2/3 portion (Cohort 1) of an ongoing clinical trial, C4591007; Among Cohort 1 participants, 95.1% had safety follow-up ≥2 months after Dose 2 at the time of the September 6, 2021 data cutoff. Safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients from the Phase 2/3 portion of the trial (Cohort 2) were provided for assessment of SAEs and other AEs of interest (e.g., myocarditis, pericarditis, anaphylaxis); the median duration of follow-up was 2.4 weeks post Dose 2 at the time of the October 8, 2021 data cutoff for Cohort 2.

Immunobridging success criteria were met for geometric mean neutralizing antibody titers and seroresponse rates at 1 month post-Dose 2 against the USA_WA1/2020 reference strain, as assessed by 50% mNG microneutralization assay, among children 5-11 years of age in study C4591007 Cohort 1 compared to study participants 16-25 years of age randomly selected from study C4591001. Subgroup immunogenicity analyses by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo). Lastly, in a supplemental descriptive efficacy analysis,

VE against symptomatic COVID-19 after 7 days post Dose 2 as of the October 8, 2021 data cutoff was 90.7% (2-sided 95% CI: 67.4%, 98.3%) in participants 5-11 years of age without prior evidence of SARS-CoV-2 infection; 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group. All cases of COVID-19 occurred in participants 5-11 years of age without prior history of SARS-CoV-2 infection, and most occurred during July-August 2021. At the time of data cutoff, no cases met the criteria for severe COVID-19 infection.

Solicited local and systemic ARs generally occurred more frequently after Dose 2, and the most commonly reported solicited ARs were pain at the injection site (71%), fatigue (39.4%), and headache (28%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset. The most frequently reported unsolicited AE in BNT162b2 recipients was lymphadenopathy (n=13; 0.9%). More BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily rash and dermatitis) than placebo recipients (n=4; 0.53%). Overall, from the combined safety database of 3,109 BNT162b2 participants, 4 BNT162b2 participants reported a SAE, and all of the SAEs were considered unrelated to vaccination. One BNT162b2 recipient withdrew from the study due to fever (40.1ºC) that occurred 2 days after Dose 1 and neutropenia that had worsened from baseline; the neutropenia was related to a pre-existing condition. There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions.

8 BENEFIT-RISK ASSESSMENT FOR CHILDREN 5-11 YEARS OF AGE

FDA conducted a benefit-risk assessment for use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5-11 years of age. The key benefits assessed include preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) visits and deaths due to COVID-19. The key risks include excess myocarditis/pericarditis cases, and related hospitalizations, ICU admissions, and deaths attributable to myocarditis/pericarditis. The benefits and risks are assessed per million fully vaccinated individuals with and without stratification by sex, and with comparison to age groups 12-15 years and 16-17 years.

The model assesses the benefits of vaccine protection in a 6-month period after completion of the primary series. The model assumes vaccine efficacy of 70% against COVID-19 cases and 80% against COVID-19 associated hospitalization based on real-world data for ages 20+ years during circulation of the Delta variant.[48] The incidence rates of COVID-19 cases for the week of September 11, 2021 are obtained from COVID-NET for all sex/age groups. COVID-NET covers approximately 10 percent of the U.S. population. Four-week averages of incidence rate for hospitalizations (week ending on 8/21/2021 to week ending on 9/11/2021) are used due to the variability in rates given the small numbers of hospitalizations per age/sex group. Estimates for the percentage of hospitalizations resulting in ICU admission and the percentage of hospitalized patients who die are based on cumulative rates of hospitalizations, ICU admissions, and deaths for each sex/age groups reported in COVID-NET since March 2020. The death rate among 5-11 year-olds is lower in COVID-NET than in other national data sources such as the CDC COVID-19 Data Tracker. This could be due to geographic differences between COVID-NET's reporting areas and the recent trajectory of the pandemic. This difference will lead to a conservative estimate of benefits in the model. The model assumes the incidence rates of COVID-19 cases and hospitalizations remain constant over the assessment period of 6 months. The estimates for excess myocarditis/pericarditis among fully vaccinated individuals ages 12-15 years and ages 16-17 years are based on data from Optum health claim database for the period 12/10/2020 –

07/10/2021, which is a conservative approach that includes non-confirmed cases. For this analysis the estimate for ages 12-15 years is applied to ages 5-11 years because vaccine-associated myocarditis/pericarditis data is not available for this age group. The proportions of vaccine-attributable myocarditis/pericarditis hospitalizations and ICU admissions are obtained from Vaccine Safety Datalink (12-17 year-old group[49]). Some of these hospitalizations and ICU admissions may be precautionary and therefore not clinically equivalent to COVID-19 hospitalizations and ICU admissions. The dose intended for use in children 5-11 years of age (10 µg), is lower than the dose used under EUA in adolescents 12-15 years of age (30 µg), and the observed systemic reactogenicity associated with the respective antigen contents in clinical trials is lower for children 5-11 years of age as well. Thus, assuming the same rate of vaccine-associated myocarditis for children 5-11 years of age as has been observed for adolescents 12-15 years of age in Optum may be a conservative overestimate.

The model results indicate that the benefits of the vaccine are highly dependent on the incidence of COVID-19. To account for uncertain dynamics of the pandemic, the benefits and risks were assessed under six scenarios: Scenario 1 with COVID-19 incidence as of September 11, 2021, Scenario 2 with COVID-19 incidence close to the recent peak of the Delta variant surge at the end of August 2021, Scenario 3 with COVID-19 incidence close to the lowest recorded incidence in June 2021, Scenario 4 with the same COVID-19 incidence as Scenario 1 and an assumption of 90% vaccine efficacy against cases and 100% efficacy against hospitalizations based on the preliminary descriptive efficacy analysis from study C4591007 Phase 2/3 Cohort 1, Scenario 5 with a 3x multiple of the death rate to more closely match the cumulative death rate for 5-11 years old seen in CDC Data Tracker, and Scenario 6 with the same COVID-19 incidence and assumed vaccine efficacy as Scenario 1 but 50% of the myocarditis cases as Scenario 1.

The results of the benefit-risk assessment are summarized in Table 14 below. The results predict that under Scenarios 1 (Sept 11, 2021 Incidence), 2 (Delta surge peak incidence), 4 (high efficacy), and 5 (higher COVID-19 death rate, per the CDC COVID-19 Data Tracker), the benefits of the Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series clearly outweigh the risks for ages 5-11 years. Under Scenario 3 (lowest incidence), the model predicts more excess hospitalizations due to vaccine-related myocarditis/pericarditis compared to prevented hospitalizations due to COVID-19 in males and in both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis/pericarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks under this lowest incidence scenario. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

Table 14. Model-Predicted Benefit-Risk Outcomes of Scenarios 1-6 per One Million Fully Vaccinated Children 5-11 Years Old

	Benefits				Risks			
Sex	**Prevented COVID-19 Cases**	**Prevented COVID-19 Hospitalizations**	**Prevented COVID-19 ICU Admissions**	**Prevented COVID-19 Deaths**	**Excess Myocarditis Cases**	**Excess Myocarditis Hospitalizations**	**Excess Myocarditis ICU Admissions**	**Excess Myocarditis Deaths**
Males & Females								
Scenario 1	45,773	192	62	1	106	58	34	0
Scenario 2	54,345	250	80	1	106	58	34	0
Scenario 3	2,639	21	7	0	106	58	34	0
Scenario 4	58,851	241	77	1	106	58	34	0
Scenario 5	45,773	192	62	3	106	58	34	0
Scenario 6	45,773	192	62	1	53	29	17	0
Males only								
Scenario 1	44,790	203	67	1	179	98	57	0
Scenario 2	54,345	250	82	1	179	98	57	0
Scenario 3	2,639	21	7	0	179	98	57	0
Scenario 4	57,857	254	83	1	179	98	57	0
Scenario 5	44,790	203	67	3	179	98	57	0
Scenario 6	44,790	203	67	1	89	49	29	0
Females only								
Scenario 1	45,063	172	54	1	32	18	10	0
Scenario 2	54,345	250	78	2	32	18	10	0
Scenario 3	2,639	21	7	0	32	18	10	0
Scenario 4	57,938	215	67	2	32	18	10	0
Scenario 5	45,063	172	54	4	32	18	10	0
Scenario 6	45,063	172	54	1	16	9	5	0

Scenario 1: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 2: COVID-19 incidence at peak of U.S. Delta variant surge at end of August 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 3: COVID-19 incidence as of nadir in June 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 4: COVID-19 incidence as of September 11, 2021, VE 90% vs. COVID-19 cases and 100% vs. COVID-19 hospitalization.
Scenario 5: COVID-19 case incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19. hospitalization, COVID-19 death rate 300% that of Scenario 1.
Scenario 6: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization, excess myocarditis cases 50% of Scenario 1.

9 PHARMACOVIGILANCE ACTIVITIES

Pfizer submitted a revised Pharmacovigilance Plan (PVP) to monitor safety concerns that could be associated with BNT162b2 in individuals 5-11 years of age. The PVP includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD).

Pfizer-BioNTech plans to conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine, including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); COVID-19 disease resulting in hospitalization or death; multisystem inflammatory syndrome (MIS)
- Adverse event reporting in accordance with regulatory requirements for the licensed vaccine, COMIRNATY
- Additionally, following approval of COMIRNATY, the Sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies, that would be modified to encompass the evaluation of children 5-11 years of age include active surveillance safety studies using large health insurance claims and/or electronic health record database(s):

  – Study C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States

    Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general U.S. population of all ages, pregnant women, the immunocompromised, and persons with a prior history of COVID-19 within selected data sources participating in the U.S. Sentinel System.

  – Study C4591021: Post-conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

    Objective: To assess the potential increased risk of AESIs, including myocarditis/pericarditis, after being vaccinated with at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

  – Study C4591021 Substudy: Substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

    Objective: To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within one year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.

  – Study C4591036: Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network [PHN]). Working title: *Myocarditis/pericarditis follow-up study within the Pediatric Heart Network*

    Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.

Pfizer-BioNTech also plans to include vaccine effectiveness analyses among individuals 5-11 years of age in Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California.”

10 TOPIC FOR VRBPAC DISCUSSION

The VRBPAC will convene on October 26, 2021, to discuss whether based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age.

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12 APPENDIX: C4591007 PHASE 1 (DOSE RANGING) – SUMMARY OF SAFETY AND IMMUNOGENICITY

During study C4591007 Phase 1, BNT162b2 was evaluated in U.S. children who were not at high risk of SARS-CoV-2 exposure, did not have medical conditions that represented risk factors for severe COVID-19, and did not have serologic/virologic evidence of SARS-CoV-2 infection. BNT162b2 dosages of 10 µg, 20 µg, then 30 µg were evaluated sequentially (n=16 participants per dosage) based upon the safety evaluation and recommendation by the internal review committee (IRC) to either advance to the subsequent dosage or terminate a specific dosage. Safety evaluation was the same as for Phase 2/3. SARS-CoV-2 50% neutralizing GMTs (SARS-CoV-2 mNG microneutralization assay) were assessed at 7 days after Dose 2.

Altogether, 48/49 (98%) of participants (assigned to the 10 µg, 20 µg, or 30 µg dosage groups combined) received two doses of BNT162b2 and completed the 1 month follow-up visit after Dose 2. One BNT162b2 participant (20 µg dosage group) did not receive study vaccine. Following safety review of reactogenicity data from the initial 4 participants in the BNT162b2 30 µg dosage group, the IRC recommended to discontinue the 30 µg dosage, due to high frequencies of solicited ARs, and recommended that the remaining 12 participants receive the

dosage selected for Phase 2/3 (i.e., 10 μg) at Dose 2. No participants from Phase 1 withdrew or discontinued from the study.

The frequencies of local and systemic adverse reactions were generally dose number and dosage dependent. Across dosages, systemic adverse reactions were generally mild and moderate in severity and resolved within 1 day of onset. No SAEs, deaths or AEs leading to withdrawal occurred at the time of data cutoff on July 16, 2021, with approximately 3 months of follow-up. No participants reported anaphylaxis, myocarditis/pericarditis, or MIS-C. One BNT162b2 (30 μg) recipient reported Grade 1 axillary lymphadenopathy, which started 3 days after Dose 2 and resolved 17 days later; the AE was considered by the study investigator to be related to study intervention.

All four participants who received 30 μg for both doses developed mild-moderate redness and pain at the injection site, and 2 of the 4 participants developed swelling. In addition, all four subjects reported fevers to 38.9ºC with mild to moderate fatigue, and 2 of the 4 developed muscle pain of moderate severity following the second dose. One participant in the 20 μg group reported Grade 3 pyrexia (temperature to 39.7º C, also reported as a systemic adverse reaction, on Day 2 post-Dose 2), which resolved by Day 3. Both 10 and 20 μg dosages elicited similar immune responses 7 days after Dose 2. In participants 5-11 years of age without evidence of SARS-CoV-2 infection up to 1 month post-Dose 2, the neutralizing antibody GMTs (NT50) at 1 month after Dose 2 were similar in the BNT162b2 10 μg and 20 μg groups (4163 and 4728, respectively).

The higher frequencies of solicited adverse reactions in participants receiving the 20 μg and 30 μg dosages, the favorable AE profile at the 10 μg dosage in participants 5-11 years of age followed for approximately 3 months after Dose 2, and the immunogenicity results demonstrating similar neutralizing antibody responses at the 10 and 20 μg dosages informed the Internal Review Committee's decision to discontinue the 30 μg dosage and proceed to Phase 2/3 at the 10 μg dosage.

Exhibit 5

Emergency Use Authorization (EUA) for an Unapproved Product
Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request) Amendment
Application Number	EUA 27034, Amendment 324
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	October 6, 2021
Receipt Date	October 6, 2021
Signatory Authority	Peter Marks, M.D., Ph.D., Director, CBER, and Acting Director, CBER/OVRR
Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA Laura Gottschalk, Ph.D., Regulatory Project Manager, OVRR/DVRPA Leslie Ball, M.D., Clinical reviewer, OVRR/DVRPA Ye Yang, Ph.D., Biostatistics reviewer, OBE/DB Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP Deborah Thompson, M.D., MSPH, PVP reviewer, OBE/DE Hong Yang, Ph.D., Benefit-risk assessment reviewer, OBE/ABRA Osman Yogurtcu, Ph.D., Benefit-risk assessment reviewer, OBE/ABRA Patrick Funk, Ph.D., Benefit-risk assessment reviewer, OBE/ABRA Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ Gregory Price, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ CAPT Oluchi Elekwachi, PharmD, MPH, Labeling reviewer, OCBQ/DCM/APLB Kanaeko Ravenell, MS, SBB, BIMO reviewer, OCBQ/DIS
Review Completion Date	October 29, 2021
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension (10 µg BNT162b2) for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	ndividuals 5 through 11 years of age

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1 EXECUTIVE SUMMARY

On October 6, 2021, Pfizer submitted a request to FDA to amend its emergency use authorization (EUA) to expand use of Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) for prevention of COVID-19 caused by SARS-CoV-2 in individuals 5 through 11 years of age (hereafter 5-11 years of age). The proposed dosing regimen is a 2-dose primary series, 10 µg mRNA/per dose, administered 3 weeks apart. To provide a vaccine with an improved stability profile and greater ease of use at vaccine distribution sites, authorization was also requested for a modified formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses a tromethamine (Tris)/Sucrose buffer instead of the phosphate-buffered saline (PBS)/Sucrose buffer as used in the previous formulation. Analytical comparability assessment, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness of the product, demonstrated that the Tris/Sucrose formulation is comparable to the previously authorized/ approved BNT162b2 PBS/Sucrose formulation.

Pfizer's EUA request includes safety data from 5-11-year-old participants in the Phase 2/3 portion of the ongoing randomized, observer-blinded, placebo-controlled clinical trial C4591007. The request initially included safety data from 1,518 recipients of BNT162b2 and 750 recipients of saline placebo, over 95% of whom had ≥2 months of safety follow-up after Dose 2 (Cohort 1; data cut-off September 6, 2021). To allow for more robust assessment of serious adverse events and adverse events of interest (e.g., myocarditis, pericarditis, anaphylaxis), Pfizer subsequently provided safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients who were enrolled into the trial later and whose median duration of follow-up was 2.4 weeks post-Dose 2 (Cohort 2; data cut-off October 8, 2021).

Vaccine effectiveness was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) among study participants 5-11 years of age (Phase 2/3 Cohort 1 of study C4591007) compared to those among a randomly selected subset of study participants 16-25 years of age (Phase 2/3 of study C4591001). The immunogenicity analyses evaluated neutralizing antibody titers against the USA_WA1/2020 reference strain, as assessed by microneutralization assay, among study participants with no evidence of prior SARS-CoV-2 infection up to 1 month post-Dose 2. Immunobridging endpoints and statistical success criteria were as follows:

- SARS-CoV-2 neutralizing antibody geometric mean titers (GMTs) measured 1 month after Dose 2, with immunobridging success criteria of >0.67 for the lower bound of the 95% confidence interval around the GMT ratio (5-11 years of age / 16-25 years of age), and a point estimate of the GMT ratio ≥1.0.

- Percentage of participants with seroresponse (≥4-fold rise from baseline [pre-Dose 1]), with immunobridging success criterion of >-10% for the lower bound of the 95% confidence interval around the difference (5-11 years of age minus 16-25 years of age) in seroresponse rates.

Immunobridging statistical success criteria, as described above, were met. Subgroup analyses of immunogenicity by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on an exploratory 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference

strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo) with no evidence of SARS-CoV-2 infection up to 1 month post-Dose 2.

In a supplemental descriptive efficacy analysis, vaccine efficacy (VE) against symptomatic COVID-19 after 7 days post-Dose 2 up to October 8, 2021 (data cut-off) was 90.7% (2-sided 95% CI: 67.7%, 98.3%) in participants 5-11 years of age without evidence of prior SARS-CoV-2 infection. Totals of 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group, most of which occurred during July-August 2021 when the Delta variant was prevalent in the United States. At the time of the data cut-off, none of these cases met the criteria for severe COVID-19.

Solicited local and systemic adverse reactions (ARs) were more frequently reported after Dose 2. The most commonly reported solicited ARs following administration of any primary series dose were pain at the injection site (84.3%), fatigue (51.7%), and headache (38.2%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and most resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1, lymphadenopathy was reported in 13 BNT162b2 recipients (0.9%); in Cohort 2, lymphadenopathy was reported in 6 BNT162b2 recipients (0.4%). In Cohort 1, more BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) than placebo recipients (n=4; 0.53%). For Cohort 2, hypersensitivity reactions were reported in 9 participants (0.6%) in the BNT162b2 group; events included a Type IV hypersensitivity reaction and other rashes. Regarding serious adverse events (SAEs), one event (fracture) was reported in Cohort 1 and 3 events (infective arthritis, foreign body ingestion, and epiphyseal fracture) were reported in Cohort 2; all were considered by the study investigator and FDA as unrelated to vaccination. There were no reports of myocarditis/pericarditis or anaphylaxis, and no deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences as compared with the overall study population, although some subgroups were too small to draw meaningful conclusions.

FDA conducted a quantitative benefit-risk analysis to evaluate predicted numbers of symptomatic COVID-19 cases, hospitalizations, ICU admissions, and deaths that would be prevented per million fully vaccinated children 5-11 years of age over a 6-month period, as compared with predicted numbers of vaccine-associated excess myocarditis cases, hospitalizations, ICU admissions and deaths per million fully vaccinated children 5-11 years of age. The model conservatively assumed that the risk of myocarditis/pericarditis associated with the 10 µg dose in children 5-11 years of age would the same as the estimated risk associated with the 30 µg dose in adolescents 12-15 years of age from Optum healthcare claims data. While benefits of vaccination were highly dependent on COVID-19 incidence, the overall analysis predicted that the numbers of clinically significant COVID-19-related outcomes prevented would clearly outweigh the numbers of vaccine-associated excess myocarditis cases over a range of assumptions for COVID-19 incidence. At the lowest evaluated COVID-19 incidence (corresponding to the June 2021 nadir), the predicted number of vaccine-associated myocarditis cases was greater than the predicted number of COVID-19 hospitalizations prevented for males and for both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks even under this low incidence scenario, which incorporates very conservative assumptions. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

At the VRBPAC meeting held on October 26, 2021, the Committee discussed and then voted on whether, based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age. The vote was 17-0 in favor of the authorization, with 1 abstention.

Based on the totality of the scientific evidence available at this time to support the conclusion that the Pfizer-BioNTech COVID-19 vaccine may be effective, and that the known and potential benefits outweigh the known and potential risks associated with the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age, the review team recommends authorization of the Pfizer-BioNTech COVID-19 vaccine under EUA for use as a 2-dose series (10 µg each dose, 3 weeks apart) in children 5-11 years of age.

2 SARS-COV-2 VIRUS AND COVID-19 DISEASE

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death. Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults, but are generally milder, with fever and cough most commonly reported.[1,2] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[3] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.[4,5] However, COVID-19 associated hospitalizations and deaths have occurred in children (see below), and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.[6]

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 15, 2021, has caused approximately 239 million cases of COVID-19, including 4.8 million deaths worldwide.[7] In the United States, more than 44 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 722,000 deaths. [8,9] Of the total COVID-19 cases reported in the United States to date, 22.3% occurred among individuals <18 years of age, with 8.7% occurring among 5-11-year-olds.[10] Following emergency use authorization of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021; however, beginning in late June 2021 a rise in cases was observed, including in children, associated with the highly transmissible Delta variant that is now predominant in the United States.[11] As of the week ending October 2, 2021, the Delta variant comprised greater than 99% of tested strains in the United States.[12] During the last week in August 2021, new COVID-19 infections in individuals less than 18 years of age surpassed those in adults 18 to 64 years of age for the first time during the pandemic.[13] In the United States, COVID-19 cases occurring in children 5-11 years now constitute 39% of cases in individuals younger than 18 years of age.[14] Among cases of

COVID-19 in individuals less than 18 years of age from the COVID-NET network[a], approximately 4,300 have resulted in hospitalization.[15] As of October 17, 2021, 691 deaths from COVID-19 have been reported in the United States in individuals less than 18 years of age, with 146 deaths in the 5-11 year age group.[16]

The most common underlying medical conditions among hospitalized children were chronic lung disease (29%), obesity (25%) and neurologic disorders (23%). A total of 68% of hospitalized children had more than one underlying condition. Obesity and feeding tube dependence were associated with increased risk of severe disease. Available evidence suggests that highest risk groups include children with special healthcare needs, including genetic, neurologic, metabolic conditions, or with congenital heart disease.[17] As in the adult population, COVID-19 in children disproportionally affects underrepresented racial and ethnic groups, with hospitalizations and deaths more frequent among Native American/Alaskan, Hispanic or Latin American, and non-Hispanic Black children than among White children.[18,19]

Following observation of an increased incidence of myocarditis in 2020 compared with 2019, several studies have suggested an association between COVID-19 and myocarditis.[20,21] While the overall incidence of myocarditis following COVID-19 infection is low, persons with COVID-19 have a nearly 16-fold increase in risk for myocarditis, compared to individuals without COVID-19. The risk is lowest among individuals 25-39 years and higher in persons less than 16 years and older than 50 years of age.[22] Myocarditis may also present as part of the multisystem inflammatory syndrome in children (MIS-C), usually 3 to 5 weeks after a SARS-CoV-2 infection. MIS-C is a rare but serious COVID-19-associated condition that occurs in less than 1% of children with confirmed SARS-CoV-2 infection.[23] MIS-C presents with persistent fever, laboratory evidence of inflammation, and at least 2 affected organs. In severe cases, hypotension and shock can occur. Most patients have laboratory markers indicating damage to the heart.[24] During the pandemic, a rise in MIS-C cases has generally lagged behind a rise observed in COVID-19 infections by several weeks,[25] with one study demonstrating the peak in MIS-C cases occurring 31 days following the peak in laboratory-confirmed COVID-19 cases.[26] Between May 2020 and October 4, 2021, the CDC received reports of 5,217 cases and 46 deaths that met the definition for MIS-C; the median age of participants was 9 years with half of the cases occurring in children ages 5 to 13 years. Males comprised 60% of cases, and 61% were reported in children who were reported as Hispanic or Black.[27] Up to 66.7% of patients with MIS-C had cardiac involvement, [28] including left ventricular dysfunction, mitral or tricuspid regurgitation, coronary artery aneurysms, and/or arrhythmias.[29] One study of outcomes in children with MIS-C followed up to 9 months found that while 76% children with MIS-C required ICU admission and therapy with inotropes or pressors; most symptoms, including cardiovascular manifestations, resolved within 1 to 4 weeks.[30] Limited data are available on long-term outcomes in MIS-C.

While children and adolescents appear less susceptible to SARS-CoV-2 infection and generally have a milder COVID-19 disease course as compared with adults,[31,32] adolescents and adults have similar SARS-CoV-2 viral loads in their nasopharynx, so adolescents may play a role in community transmission.[33,34] Transmission of SARS-CoV-2 virus from children can occur in both household and school settings.[35,36] In schools, transmission depends on the transmission rates locally, variants circulating in the community, vaccination rates, and other preventive mitigation

[a] COVID-NET covers approximately 10% of the U.S. population; The current network covers nearly 100 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and four additional states through the Influenza Hospitalization Surveillance Project (IA, MI, OH, and UT); see https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html.

strategies. Transmission between school staff members may be more common than transmission involving students.[37] There is evidence that SARS-CoV-2 transmission is greater in secondary and high schools than elementary schools.[38,39] Outbreaks of COVID-19 have been reported in settings where children congregate, such as summer youth camps.[40,41]

In addition to morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education). Other impacts of COVID-19 on children include limited access to basic services such as healthcare and child protective services, and social isolation due to disruption of school, sports, and social group gatherings. The emergence of the Delta variant, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. While recently reported cases appear to be declining relative to the Delta variant-associated peak globally and in the United States, the longer-term effect of the Delta variant and the potential role of other variants on the future course of the pandemic is uncertain.

3 AUTHORIZED AND APPROVED VACCINES AND THERAPIES FOR COVID-19

FDA has issued EUAs for three COVID-19 vaccines as shown in Table 1 below. The Pfizer-BioNTech COVID-19 Vaccine is also FDA approved for use as a 2-dose primary series in individuals 16 years of age and older, under the trade name COMIRNATY (see Section 4).

Table 1. Emergency Use Authorizations of COVID-19 Vaccines

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Pfizer-BioNTech	2-dose primary series (3 weeks apart)	Individuals ≥16 years of age	December 11, 2020
		Individuals ≥12 years of age	May 10, 2021
Pfizer-BioNTech	3rd primary series dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021
Pfizer-BioNTech	Booster dose (at least 6 months after completing a primary series of COMIRNATY and/or Pfizer-BioNTech COVID-19 Vaccine)	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	September 22, 2021
Moderna	2-dose series (4 weeks apart)	2-dose primary series in adults ≥18 years of age	December 18, 2020
Moderna	3rd dose (at least 1 month after the second dose)	Individuals ≥12 years of age with compromised immune systems due to solid organ transplantation or conditions considered to have an equivalent level of immunocompromise	August 12, 2021

Sponsor	Authorized Use (Interval)	Indicated Population	Date of EUA or EUA Amendment
Moderna	Booster dose (at least 6 months after completing a primary series of Moderna COVID-19 Vaccine	• Individuals 65 years of age and older • Individuals 18 through 64 years of age and at high risk of severe COVID-19 • Individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2	October 20, 2021
Janssen	Single dose	Individuals ≥18 years of age	February 27, 2021
Janssen	Booster dose	Individuals ≥18 years of age	October 20, 2021
Pfizer, Moderna and Janssen	Single heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (same interval as authorized for a booster dose of the vaccine used for primary vaccination)	Same population(s) as those eligible to receive a booster dose of the vaccine used for primary vaccination	October 20, 2021

Remdesivir is the only product currently approved by the FDA for treatment of COVID-19 requiring hospitalization, and its approved use is limited to individuals 12 years of age and older. Prior to its approval, remdesivir was authorized for emergency use in adults and pediatric patients and remains authorized for emergency use in hospitalized pediatric patients who are not included in the indicated population under licensure.

Emergency use authorizations of COVID-19 pharmacological products for post-exposure prophylaxis and/or treatment of COVID-19 are as follows:

Table 2. Emergency Use Authorized Pharmacological Products for Post-exposure Prophylaxis and/or Treatment of COVID-19

Product	Date of EUA	Authorized Use and Population
SARS-CoV-2-targeting Monoclonal Antibodies		
• Bamlanivimab/etesevimab • Sotrovimab • Casirivimab/imdevimab	Reissued September 16, 2021 May 26, 2021 Reissued September 9, 2021	All three products are indicated for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years and older at high risk for progressing to severe COVID-19[a] Casirivimab/imdevimab is also authorized for post-exposure prophylaxis (prevention) for COVID-19 in patients at high risk for progressing to severe COVID-19[b]
Antiviral Drugs		
• Remdesivir	Reissued October 22, 2020 (following FDA approval in adults and some pediatric patients)	Treatment of COVID-19 in hospitalized pediatric patients weighing at least 3.5 kg to <40 kg, or <12 years of age weighing at least 3.5 kg, or ≥12 years and weighing at least 40 kg

Product	Date of EUA	Authorized Use and Population
Immune Modulators		
• Baricitinib	Reissued July 29, 2021	Treatment of COVID-19 in hospitalized patients[b] receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
• Actemra	June 24, 2021	
COVID-19 Convalescent Plasma	Reissued March 9, 2021	Treatment of hospitalized patients with COVID-19

a Indicated for adults and pediatric patients 12 years of age and older weighing at least 40 kg
b Indicated for adults and pediatric patients 2 years and older
ECMO extracorporeal membrane oxygenation, EUA emergency use authorization
Source: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs Accessed August 2, 2021.

4 COMIRNATY (COVID-19 VACCINE, mRNA)

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.). COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two doses (0.3 mL each) 3 weeks apart, with each dose containing 30 µg mRNA. COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19. COMIRNATY is also authorized under EUA for use as a 2-dose primary series in individuals 12 years of age and older, for use as a third primary series dose in individuals 12 years of age and older with certain immunocompromising conditions, and for use as a single booster dose administered at least 6 months after completion of a primary series to individuals 65 years of age and older, individuals 18 through 64 years of age at increased risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The vaccine authorized under EUA is also known as the Pfizer-BioNTech COVID-19 Vaccine. During clinical development, the vaccine was called BNT162b2.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately and is stored at 20°C to 25°C. The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contains six doses of 0.3 mL of vaccine. COMIRNATY does not contain preservative.

4.1 Efficacy of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

Efficacy of BNT162b2 for the prevention of COVID-19 occurring at least 7 days after completion of a 2-dose primary series was evaluated in an ongoing Phase 3 study, C4591001, in approximately 44,000 participants randomized 1:1 to receive two doses of either BNT162b2 or placebo, 3 weeks apart. Participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age). The population for the VE analysis that supported approval of COMIRNATY included participants 16 years of age and older who

had been enrolled from July 27, 2020, and who were followed for the development of COVID-19 during blinded placebo-controlled follow-up through as late as March 13, 2021. Overall, 60.8% of participants in the BNT162b2 group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after the primary series in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in subjects without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in subjects with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

4.2 Safety of a 2-dose primary series of COMIRNATY in individuals 16 years of age and older

In study C4591001, the most commonly reported solicited adverse reactions (occurring in ≥10% of participants) among BNT162b2 vaccine recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported solicited adverse reactions in BNT162b2 vaccine recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

Among participants 16 through 55 years of age, SAEs from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 0.8% of BNT162b2 recipients and 0.9% placebo recipients. In a similar analysis, in participants 56 years of age and older serious adverse events (SAEs) were reported by 1.8% of BNT162b2 recipients and 1.7% of placebo recipients who received at least 1 dose of BNT162b2 or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of follow-up after the primary series. There were no notable patterns between treatment groups for specific categories of SAEs (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to BNT162b2. From Dose 1 through the March 13, 2021 data cut-off date, there were a total of 38 deaths, 21 in the BNT162b2 group and 17 in the placebo group. None of the deaths were considered related to vaccination.

4.3 Effectiveness and safety of a 2-dose primary series of Pfizer-BioNTech COVID-19 Vaccine in adolescents 12-15 years of age

On May 10, 2021, FDA authorized the use of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age based on safety and effectiveness data from an ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 2,260 participants 12-15 years of age.

Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race and sex. In the supplemental efficacy analysis, VE after 7

days post-Dose 2 was 100% (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0% (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provided compelling direct evidence of clinical benefit in addition to the immunobridging data.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of greater than 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local and systemic adverse reactions occurred in up to 2.4% of 12-15-year-old BNT162b2 recipients, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. No deaths were observed in this age group during the follow-up period. SAEs, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious AEs among study participants 12-15 years of age that would suggest a causal relationship to BNT162b2 vaccine.

4.4 Cases of myocarditis/pericarditis reported in BNT162b2 recipients in ongoing clinical trials of BNT162b2

Pericarditis and myopericarditis have been reported in BNT162b2 recipients in study C4591001:

- A male participant ≥55 years of age, with no medical history, reported pericarditis 28 days after Dose 2 of BNT162b2; the event was assessed by the investigator and FDA as not related to the study intervention and was ongoing at the time of the data cut-off.
- A male participant who was randomized to blinded placebo group at age 15 years and subsequently unblinded and crossed over to open label BNT162b2 at age 16 years was diagnosed with myopericarditis beginning 2 days after Dose 2 of BNT162b2. He was hospitalized on Day 3 and treated with IVIG, non-steroidal anti-inflammatory medications and steroids, and discharged the following day. He was followed by a cardiologist and seen for follow up 2 months after vaccination. At that time the cardiologist recommended limited activity. The investigator concluded that the there was a reasonable possibility that the myopericarditis was related to vaccine administration due to the plausible temporal relationship. FDA agrees with this assessment.

4.5 Post-EUA and post-licensure surveillance

As of October 21, 2021, more than 244 million doses of the Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. According to the CDC COVID Data Tracker, 205,046 individuals less than 12 years of age have received at least one dose of the Pfizer-BioNTech

COVID-19 Vaccine, and 125,656 have received two doses. It is not known what proportions of these numbers represent unauthorized use of the vaccine and what proportions might reflect errors in reporting of the recipients' ages.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the Pfizer-BioNTech COVID-19 Vaccine, and the results are summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine.

As of October 18, 2021, VAERS received 442,763 reports (including 270,342 U.S. reports), of which 854 U.S. reports were described as involving children 5-11 years of age, 9,523 U.S. reports were in children 12-15 years of age, and 5,821 U.S. reports were in adolescents 16-17 years of age. The top ten most frequently reported MedDRA Preferred Terms (PTs) included:

- Overall, most frequent PTs: headache, fatigue, pyrexia, SARS-CoV-2 test, dizziness, pain, nausea, chills, pain in extremity, dyspnoea
- Most frequent PTs in in persons ≤17 years of age: dizziness, syncope, headache, pyrexia, nausea, product administered to patient of inappropriate age, chest pain, fatigue, vomiting, loss of consciousness.

Note that a report may have one or more PTs. An additional query of VAERS for U.S. reports by dose number retrieved the following: 127,747 reports after Dose 1; 100,730 reports after Dose 2; and 5,223 reports after dose 3 (data as of October 18, 2021).

Safety concerns identified from post-authorization safety surveillance data in VAERS are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets. Review of passive surveillance AE reports and the Sponsor's periodic safety reports did not indicate any new safety concerns, including in adolescents. Most AEs are labeled events and consistent with the safety profile for this vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest a new safety concern, including among the reports described as involving children 5-11 years of age.

Anaphylaxis

Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[42][43] Anaphylaxis is an important identified risk in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The estimated crude reporting rate for anaphylaxis in the U.S. is 6.1 cases per million doses at this time based on the above VAERS data.

Myocarditis and pericarditis

Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis, particularly within 7 days following administration of the second dose of the 2-dose primary series. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among males under 40 years of age than among

females and older males and have been highest in males 12 through 17 years of age (~71.5 cases per million second primary series doses among males age 16-17 years and 42.6 cases per million second primary series doses among males age 12-15 years as per CDC presentation to the ACIP on August 30, 2021). In an FDA analysis of the Optum healthcare claims database, the estimated excess risk of myocarditis/pericarditis approached 200 cases per million fully vaccinated males 16-17 years of age and 180 cases per million fully vaccinated males 12-15 years of age.[44] Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Myocarditis and pericarditis were added as important identified risks in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

5 EUA AMENDMENT REQUEST FOR THE PFIZER-BIONTECH COVID-19 VACCINE FOR USE IN CHILDREN 5-11 YEARS OF AGE

On October 6, 2021, Pfizer and BioNTech submitted a request to amend this EUA to include use of a 2-dose primary series of the Pfizer-BioNTech COVID-19 Vaccine (10 µg each dose, administered 3 weeks apart) in individuals 5-11 years of age for active immunization to prevent COVID-19 caused by severe acute coronavirus 2 (SARS-CoV-2).

The request is accompanied by safety data from the Phase 2/3 portions of study C45910071. This data includes 518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age, of whom over 95% of participants in each group had ≥2 months of safety follow up after Dose 2 (Cohort 1, September 6, 2021 data cut-off), and data from an additional 1,591 BNT162b2 and 788 placebo recipients who were enrolled into the trial later and whose median duration of follow-up was 2.4 weeks post-Dose 2 (Cohort 2; October 8, 2021 data cut-off). Vaccine effectiveness in children 5-11 years of age was inferred by immunobridging SARS-CoV-2 50% neutralizing antibody titers (NT50, as assessed by SARS-CoV-2 mNG microneutralization assay) among C4591007 study participants 5-11 years of age following completion of a primary series to antibody titers of those of young adults 16-25 years of age who received two doses of 30 µg BNT162b2 in study C4591001. Efficacy against COVID-19 disease was assessed descriptively in study C4591007 participants 5-11 years of age.

Vaccine formulation

Authorization is being requested for a modified formulation of the Pfizer-BioNTech COVID-19 Vaccine. To provide an improved stability profile to the vaccine, the Pfizer-BioNTech COVID-19 Vaccine for use in children 5-11 years of age uses tromethamine (Tris) buffer instead of the phosphate-buffered saline (PBS) as used in the previous formulation. The packaged vials for the new formulation are also stored frozen at -90°C to -60°C; however, the frozen vials may be thawed and stored at refrigerator at 2°C to 8°C for up to 10 weeks. For the 10-µg mRNA dose, each 1.3-mL filled vial must be diluted with 1.3 mL 0.9% sodium chloride for injection to provide 10 doses at 10 µg RNA / 0.2 mL Injection volume. After dilution, the vials should be stored at 2°C to 25°C and should be used within 12 hours. See Section 8.1 Chemistry, Manufacturing, and Controls (CMC) information, for details.

6 EUA REQUIREMENTS, GUIDANCE AND CONSIDERATIONS PERTAINING TO COVID-19 VACCINES

6.1 U.S. requirements to support issuance of an EUA for a biological product

Based on the declaration by the Secretary of the U.S. Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

6.2 FDA guidance for industry related to COVID-19 vaccines

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" February 2021, originally issued October 2020).[45] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in children 5-11 years of age. The timing, design, and appropriate endpoints for pediatric studies are discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent COVID-19" from June 2020.[46]

6.3 Regulatory considerations for clinical development of COVID-19 vaccines in children

The Vaccines and Related Biological Products Advisory Committee convened on June 21, 2021, to discuss, in general, the data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

Effectiveness

Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to a young adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric mean titer [GMT] and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric vs. young adult populations.

Safety

The size of the safety database sufficient to assess risks of COVID-19 vaccines for EUA in pediatric age groups would generally be the same as for other preventive vaccines for infectious diseases, provided that no specific safety concern is identified that could reasonably be evaluated in pre-authorization clinical trials. These safety data would include characterization of common adverse reactions (reactogenicity, including injection site and systemic adverse reactions), and less common but medically important adverse reactions. Depending on prior experience with the vaccine in adults, and prior experience with licensed vaccines based on the same or similar platforms, FDA has accepted an overall pediatric safety database in the range of ~500 to ~3,000 trial participants exposed to the age-appropriate dose and regimen intended for licensure and have at least 6 months of follow-up evaluations after completion of the vaccination regimen. Since COVID-19 vaccines represent a new class of vaccines, with many of the lead candidates based on new platform technologies, an appropriate overall pediatric safety database would approach the upper end of this range, with adequate representation across all pediatric age groups, in particular younger age groups (e.g., <12 years) that are less physiologically similar to adults. A control group (ideally placebo control) would be important to inform interpretation of safety data and to comply with the expectation for adequate and well-controlled studies to support licensure. If another COVID-19 vaccine is licensed or authorized for use in the age group(s) enrolled in the trial, recommended by public health authorities, and widely available such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control.

Within the overall pre-licensure safety database, solicited reactogenicity could be adequately characterized among several hundred trial participants in each relevant age group. Additionally, safety evaluation in all trial participants would include collection of all AEs through at least 1 month after each study vaccination and collection of serious and other medically attended AEs for the duration of the trial. Although longer-term follow-up (through 1 year or longer post-vaccination) of trial participants would be important to ongoing assessment of both benefits and risks, completion of such longer-term follow-up would not be a prerequisite to licensure unless warranted by a specific safety concern. Post-licensure/post-authorization safety surveillance and observational studies in pediatric populations would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials.

7 FDA REVIEW OF CLINICAL SAFETY AND EFFECTIVENESS DATA

7.1 Overview of study C45910007

The EUA amendment request contains safety, immunogenicity, and descriptive efficacy data from children 5-11 years of age enrolled in C4591007, an ongoing Phase 1/2/3, randomized, placebo-controlled study. The comparator group for the immunobridging analyses to support vaccine effectiveness in this age group was a random subset of Phase 2/3 participants 16-25 years of age enrolled in study C4591001, the study in which VE against COVID-19 was established in individuals 16 years of age or older.

Data from study C4591007

- Phase 2/3: a total of 3,109 BNT162b2 (10 µg) recipients and 1538 placebo recipients 5-11 years of age
  - Cohort 1: 1,518 BNT162b2 (10 µg) recipients and 750 placebo recipients, of whom 1,444 (95.1%) and 714 (95.2%), respectively, had at least 2 months of safety follow-up after completing a 2-dose primary series (data cut-off September 6, 2021). Summary tables for solicited adverse reactions (ARs) and immunogenicity analyses are based on this cohort of subjects. A descriptive efficacy analysis was also based on this cohort.
  - Cohort 2: A second cohort of 1,591 BNT162b2 (10 µg) recipients and 7878 placebo recipients had a median duration of follow up of 2.4 weeks post-Dose 2 at the time of data cut-off (October 8, 2021). Safety data from this cohort were provided for further assessment of SAEs and AEs of clinical interest.
- Phase 1 data to support dosage selection for Phase 2/3 portion of the study

Table 3. Study C4591007*: Participants 5-11 Years of Age (10 µg BNT162b2)

Study Number/ Countries	Description	BNT162b2 N	Placebo (Saline) N	Study Status
C4591007 United States, Finland, Poland, and Spain	Phase 1/2/3 randomized, placebo-controlled; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Phase 1: 16 Phase 2/3: 3,109	Phase 1:0 Phase 2/3: 1,538	Ongoing

N=Number of randomized participants as of data cut-off dates July 16, 2021 (all Phase 1 participants), September 6, 2021 (Phase 2/3 cohort 1: 1,518 BNT162b2, 750 placebo; enrollment started June 7, 2021) and October 8, 2021 (Phase 2/3 cohort 2: 1,591 BNT162b2, 788 placebo; enrollment started August 26, 2021).
*First participant, first visit was March 24, 2021 (Phase 1).

7.2 Study design

Study C4591007 is an ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled safety, immunogenicity, and efficacy study. This section presents the design for the Phase 2/3 portion of the study in children 5-11 years of age. Please see Appendix 1 for Phase 1 study design.

Phase 2/3 is being conducted in the United States, Finland, Poland, and Spain. The Phase 2/3 portion of the study did not exclude children with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, children with known HIV, hepatitis B or hepatitis C, or

stable pre-existing disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment).

Participants were randomized 2:1 to receive two doses of 10 µg BNT162b2 or placebo (saline), 3 weeks apart. Participants who turned 12 years of age during the study would have the opportunity to receive the EUA-authorized dose level of 30 µg (12-15 years of age) if they originally received placebo.

Immunogenicity evaluation

Immunobridging was based on SARS-CoV-2 neutralizing antibody responses in study C4591007 Phase 2/3 (Cohort 1) participants 5-11 years of age compared to neutralizing antibody responses in a random subset of study C4591001 participants 16-25 years of age, as measured by 50% neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) against the reference strain (USA_WA1/2020) at 1 month after a primary series. The primary analysis is based on the evaluable immunogenicity population of participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2.

Primary endpoints and statistical success criteria

- Immunobridging success based on GMT was declared if the lower limit (LL) of the 95% CI for the GMT ratio (5-11 years of age / 16-25 years of age) was >0.67, and the point estimate of the GMT ratio was ≥1.0.
- Immunobridging success based on the seroresponse rate was declared if the LL of the 95% CI for the difference in seroresponse rates (5-11 years of age minus 16-25 years of age) was >-10%. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination (pre-Dose 1) to 1 month after Dose 2.

Efficacy evaluation

A secondary objective is to evaluate efficacy of BNT162b2 against laboratory-confirmed symptomatic COVID-19 occurring from 7 days after Dose 2 in participants without evidence of prior SARS CoV-2 infection and in participants with or without evidence of prior SARS CoV-2 infection. A descriptive analysis was conducted once 19 confirmed cases had accrued. COVID-19 and severe COVID-19 case definitions are included in Appendix 2.

Safety evaluation

Reactogenicity (solicited local and systemic adverse reactions)

The participants' parents or participants themselves recorded reactogenicity assessments and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain).

Unsolicited adverse events

Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after Dose 2, and SAEs from Day 1 to 6 months after Dose 2, or the data cut-off date (Phase 1: July 16, 2021; Phase 2/3: September 6, 2021). AEs were categorized by frequency and maximum severity according to MedDRA System Organ Class and PT, and relationship to the study intervention was assessed. Deaths are recorded to the end of the study.

Adverse events of clinical interest

The occurrence of certain AEs including lymphadenopathy and myocarditis/pericarditis were assessed as part of the safety review, as well as additional AEs requested by FDA (including anaphylaxis, Bell's palsy, appendicitis, pregnancy exposures and outcomes, and MIS-C cases).

Analysis populations

Pertaining to participants 5-11 years of age

- Safety: All participants who receive at least 1 dose of the study intervention.
- All-available immunogenicity: All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.
- Evaluable immunogenicity: All eligible randomized participants who receive two doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and have no other important protocol deviations as determined by the clinician.
- Evaluable efficacy: All randomized participants who receive all vaccinations as randomized, with Dose 2 received within the predefined window (within 19-42 days after Dose 1) and have no other important protocol deviations as determined by the clinician on or before 7 days after Dose 2.

Data analysis cut-off dates:

- All Phase 1 participants: July 16, 2021
- Phase 2/3 Cohort 1 (initial): September 6, 2021 (enrollment started June 7, 2021)
- Phase 2/3 Cohort 2: October 8, 2021 (enrollment started August 26, 2021)

7.3 Disposition of Phase 2/3 participants

Cohort 1 (initial enrollment)

Cohort 1 was comprised 1,538 BNT162b2 10 µg participants and 757 placebo participants; 11 (0.7%) BNT162b2 and 6 (0.8%) placebo participants did not receive any study agent. Two BNT162b2 participants (0.1%) and two placebo participants (0.3%) discontinued vaccination before the 1 month post-Dose 2 follow up; none resulted from an AE. Three participants turned 12 years of age during the course of the study and became eligible to receive 30 µg BNT162b2 under EUA; two of these participants received two doses of 10 µg BNT162b2 prior to being unblinded, and the other participant received both doses of placebo before being unblinded and withdrew to receive a COVID-19 vaccine outside of the study; data from these participants were included in endpoint analyses up to the point at which they were unblinded.

Safety population: solicited ARs, unsolicited AEs, SAEs and AEs of clinical interest were assessed in a total of 2,268 (1,518 10 µg BNT162b2, 750 placebo) participants 5-11 years of age; over 95% of participants in each study group completed at least 2 months of safety follow-up after Dose 2. Five BNT162b2 recipients and six placebo recipients withdrew from the study, mainly due to voluntary withdrawal.

Comparator group for immunogenicity: The comparator group for immunobridging analyses consisted of 300 evaluable participants 16-25 years of age who received both doses of BNT162b2 30 µg and were randomly selected from study C4591001 Phase 2/3.

Table 4. Disposition of Immunogenicity Populations, Phase 2/3, Participants 5-11 Years of Age (Study C4591007 Cohort 1) and Participants 16-25 Years of Age (Study C4591001)

Disposition	5-11 years of age BNT162b2 (10 µg) n (%)	5-11 years of age Placebo n (%)	16-25 years of age BNT162b2 (30 µg) n (%)
Randomized to receive BNT162b2[a]	322 (100.0)	163 (100.0)	300 (100.0)
All-available immunogenicity population	311 (96.6)	156 (95.7)	286 (95.3)
Excluded because they did not have at least 1 valid and determinate immunogenicity result after vaccination	11 (3.4)	7 (4.3)	13 (4.3)
Evaluable immunogenicity population	294 (91.3)	147 (90.2)	273 (91.0)
Without evidence of infection up to 1 month after Dose 2[b]	264 (82.0)	130 (79.8)	253 (84.3)
Subjects excluded from evaluable immunogenicity population	28 (8.7)	16 (9.8)	27 (9.0)
Reason for exclusion (subjects may have been excluded for >1 reason)			
Did not receive 2 doses of the vaccine as randomized	3 (0.9)	1 (0.6)	0
Did not receive Dose 2 within 19 to 42 days after Dose 1	3 (0.9)	2 (1.2)	3 (1.0)
Did not have at least 1 valid and determinate immunogenicity result within 28 to 42 days after Dose 2	13 (4.0)	14 (8.6)	21 (7.0)
Did not have blood draw at 1 month after Dose 2 visit	7 (2.2)	6 (3.7)	8 (2.7)
1 Month after Dose 2 blood draw outside of window (28-42 days after Dose 2)	6 (1.9)	8 (4.9)	13 (4.3)
Had important protocol deviation(s) as determined by the clinician	10 (3.1)	0	4 (1.3)

%:n/N. n = number of participants with the specified characteristic. N = number of randomized participants in the specified group; this value is the denominator for the percentage calculations.

a. Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (i.e., N-binding ant body [serum] negative at pre-Dose 1 and at 1 month post-Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] at pre-Dose 1 and pre-Dose 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

b. Participants may have been excluded for more than 1 reason.

Efficacy population

Of 2186 participants (1450 BNT162b2 and 736 placebo) in the evaluable efficacy population, 1305 BNT162b2 and 663 placebo participants did not have evidence of SARS-CoV-2 infection from pre-Dose 1 to 7 days post-Dose 2.

Cohort 2 (expansion)

In the Phase 2/3 safety expansion, 1,598 participants were randomized to receive BNT162b2 and 796 were randomized to placebo. At the time of the October 8, 2021, cut-off, most participants (98.7%) had received both Dose 1 and Dose 2. Seven of the randomized BNT162b2 participants did not receive vaccine. One participant in the BNT162b2 group discontinued from the vaccination period due to AEs of pyrexia and neutropenia that worsened from baseline (see Section 7.7.7, AEs leading to withdrawal). Two participants (0.1%) in the BNT162b2 group withdrew from the study before the 1-month period. Neither withdrawal was due to an AE.

Comorbidities at baseline

Comorbidities were defined as described in Kim et al. MMWR 2020.[47] Participants with any comorbidity, including obesity, constituted 20.6% of the BNT162b2 group and 20.3% of placebo group. The most common comorbidities at baseline in the Cohort 1 BNT162b2 group were obesity (11.5%), asthma (7.8%), neurologic disorders (1.3%), and congenital heart disease (1.0%). Other comorbidities included diabetes in 2 participants (0.2%), and one participant each (0.1%) for acute lymphocytic leukemia (immunocompromising conditions), cystic fibrosis, and sickle cell disease.

Demographic characteristics were similar in Cohort 2 as Cohort 1. Overall, 11.1% of participants were obese. Comorbidities including obesity were found in 19.9% of participants. As in Cohort 1, the most common comorbidities were asthma, neurologic disorders and congenital heart disease.

7.4 Demographic and baseline characteristics

Demographic characteristics for the Phase 2/3 study C4591007 Cohort 1 safety population are summarized in Table 5 below. Overall, participants were predominately White, with a mean age of approximately 8 years. Of the BNT162b2 recipients, 11.5% were obese, 8.8% had evidence of prior SARS-CoV-2 infection and 20.6% had comorbidities placing them at increased risk of severe COVID-19. More than 70% of participants were enrolled in the United States.

Table 5. Demographic and Baseline Characteristics, Phase 2/3, Participants 5-11 Years, Safety Population, Study C4591007 Cohort 1

Characteristic	C4591007 BNT162b2 10 µg (N[a]=1518) n[b] (%)	C4591007 Placebo (N[a]=750) n[b] (%)
Sex: Male	799 (52.6)	383 (51.1)
Sex: Female	719 (47.4)	367 (48.9)
Race: White	1204 (79.3)	586 (78.1)
Race: Black or African American	89 (5.9)	58 (7.7)
Race: American Indian or Alaska Native	12 (0.8)	3 (0.4)
Race: Asian	90 (5.9)	47 (6.3)
Race: Native Hawaiian or other Pacific Islander	<1%	<1%
Race: Multiracial	109 (7.2)	49 (6.5)
Race: Not reported	9 (0.6)	7 (0.9)
Ethnicity: Hispanic or Latino	319 (21.0)	159 (21.2)
Ethnicity: Not Hispanic or Latino	1196 (78.8)	591 (78.8)
Ethnicity: Not reported	<1%	<1%
Age: Mean years (SD)	8.2 (1.93)	8.1 (1.97)
Age: Median (years)	8.0	8.0
Obese[c]: Yes	174 (11.5)	92 (12.3)
Obese[c]: No	1343 (88.5)	658 (87.7)
Obese[c]: Missing	<1%	<1%
Baseline Evidence of Prior SARS-CoV-2 Infection: Negative[e]	1385 (91.2)	685 (91.3)
Baseline Evidence of Prior SARS-CoV-2 Infection: Positive[f]	133 (8.8)	65 (8.7)
Comorbidities[d]: Yes	312 (20.6)	152 (20.3)
Comorbidities[d]: No	1206 (79.4)	598 (79.7)
Country: Finland	158 (10.4)	81 (10.8)
Country: Poland	125 (8.2)	60 (8.0)
Country: Spain	162 (10.7)	78 (10.4)

Characteristic	C4591007 BNT162b2 10 µg (N[a]=1518) n[b] (%)	C4591007 Placebo (N[a]=750) n[b] (%)
Country: United States	1073 (70.7)	531 (70.8)

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; NAAT = nucleic acid amplification test; N-binding = SARS-CoV-2 nucleoprotein-binding; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
a. N = number of participants in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.
c. Obese is defined as a body mass index (BMI) at or above the 95th percentile according to the growth chart. Refer to the CDC growth charts at https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm.
d. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease: defined as participants who had at least one of the prespecified comorbidities based on MMWR 69(32);1081-1088 and/or obesity (BMI ≥ 95th percentile).
e. Negative N-binding antibody result and negative NAAT result at pre-Dose 1 and no medical history of COVID-19.
f. Positive N-binding antibody result at pre-Dose 1, positive NAAT result at pre-Dose 1, or medical history of COVID-19.

The demographic and baseline characteristics of the evaluable immunogenicity and efficacy populations without baseline evidence of SARS-CoV-2 infection were similar to the overall characteristics of Cohort 1 population.

Demographic characteristics in Cohort 2 were similar to Cohort 1.

Comparator group for immunogenicity: The 300 participants ages 16-25 years from study C4591001 were from sites in the United States (64%), Argentina (18%), Brazil (12%), and South Africa/Turkey/Germany (6% combined total).

Less than 0.8% of participants in either group received non-COVID-19 vaccines during the study; most were routine pediatric immunizations including diphtheria, pertussis, tetanus, human papillomavirus vaccine, and meningococcal vaccine.

7.5 Immunogenicity results

7.5.1 Primary immunogenicity objective

Immunogenicity of BNT162b2 was assessed based on analyses of GMTs and seroresponse rates for neutralizing antibody titers to the reference strain (USA_WA1/2020).

GMTs of neutralizing antibody titers to the reference strain

Among participants in the evaluable immunogenicity population without prior evidence of SARS-CoV-2 infection up to 1 month after Dose 2, the ratio of SARS-CoV-2 50% neutralizing GMT in children 5-11 years (10 µg each dose) compared to individuals 16-25 years (30 µg each dose) was 1.04 (95% CI: 0.93, 1.18). The lower bound of the 2-sided 95%CI for GMR was >0.67 and the point estimate was ≥1, which met FDA's requested criteria; see Table 6, below.

Table 6. SARS-CoV-2 Neutralizing GMTs (NT50)[a] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[b]

GMT (95% CI) 5-11 Years of Age Study C4591007 N[c] = 264	GMT (95% CI) 16-25 Years of Age Study C4591001 N[c] = 253	GMT Ratio (95% CI) (5-11 Years of Age / 16-25 Years of Age)[d]
1197.6 (1106.1, 1296.6)	1146.5 (1045.5, 1257.2)	1.04 (0.93, 1.18)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer.
b. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
c. N = Number of Phase 2/3 participants with valid and determinate assay results for the specified assay at the given dose/sampling time point within specified window.
d. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the GMT ratio is greater than 0.67 and the point estimate of the GMT ratio is ≥1.0.

Rates of neutralizing antibody seroresponse to the reference strain

Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection up to 1 month after Dose 2 are displayed in Table 7 below. Children 5-11 years of age had similar seroresponse (as measured from before vaccination to 1 month after Dose 2) rate as individuals 16-25 years of age. The difference between the two age groups was 0.0% (95% CI: -2.0%, 2.2%). The lower limit of the 95% CI for the difference in seroresponse rate was -2.0%, which was greater than the prespecified margin of -10% and thus immunobridging based on seroresponse rate was met, see Table 7 below.

Table 7. Seroresponse Rates[a,b] at 1 Month Post-Primary Series in Phase 2/3 BNT162b2 (10 µg) Recipients 5-11 Years of Age and Study C4591001 Phase 2/3 Cohort 1 BNT162b2 (30 µg) Recipients 16-25 Years of Age[b] Without Evidence of SARS-CoV-2 Infection up to 1 Month After Dose 2, Evaluable Immunogenicity Population[c]

Seroresponse 5-11 Years of Age Study C4591007 %[d] (95% CI) N= 264	Seroresponse 16-25 Years of Age Study C4591001 %[d] (95% CI) N= 253	% Difference in Seroresponse Rate (Age Group 5-11 Years minus Age Group 16-25 Years)[e] (95% CI)
99.2 (97.3, 99.9)	99.2 (97.2, 99.9)	0 (-2.0, 2.2)

a. SARS-CoV-2 mNeonGreen virus microneutralization assay-NT50, reference strain: recombinant USA_WA1/2020.
b. Seroresponse defined as at least 4-fold rise relative to pre-Dose 1; if the baseline measurement was below LLOQ, a postvaccination titer of ≥4 × LLOQ was considered a seroresponse.
c. Evaluable immunogenicity population pertaining to Phase 2/3 BNT162b2 participants 5-11 years of age (study C4591007) and Phase 2/3 BNT162b2 participants 16-25 years of age (study C4591001).
d. %: n/N. n = number of participants with seroresponse for the given assay at the given dose/sampling time point. N = Number of subjects with valid and determinate assay results for the specified assay within the specified window for blood samples collected at baseline (pre-Dose 1) and 1 month after primary series.
e. Immunobridging statistical success is declared if the lower limit of the 2-sided 95% CI for the difference in percentages of participants with seroresponse is >-10%.

Subgroup Analyses of Geometric Mean Titers

GMTs of SARS-CoV-2 neutralizing titers and seroresponse rates at 1 month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to evaluate by protocol-specified methods. Specifically, no notable differences in GMTs or seroresponse rates were observed by age (i.e., 5-6 years vs. 7-8 years vs. 9-11 years), sex, race, ethnicity, obesity (Y/N), or SARS-CoV-2 status.

In descriptive post hoc analyses of immunogenicity data based on the presence or absence of comorbidities (defined as described in Kim et al. MMWR 2020[47]), GMT and seroresponse rates among those with comorbidities were comparable to those without comorbidities.

7.5.2 Exploratory immunogenicity analyses against the Delta Variant

In response to FDA's request for immunogenicity data to support effectiveness of a 10 µg BNT162b2 primary series against the Delta variant, Pfizer submitted exploratory descriptive analyses of data from a randomly selected subset of participants (34 BNT162b2 recipients, 4 placebo recipients) with no evidence of infection up to 1 month post-Dose 2. These data were generated using non-validated SARS-CoV-2 plaque reduction neutralization assays with the reference strain (USA-WA1/2020) and the Delta variant; the relative sensitivity of the two assays is not known.

Table 8. SARS-CoV-2 Neutralizing GMTs[a] at Pre-Dose 1 and 1 Month Post-Primary Series in C4591007 Phase 2/3 Cohort 1 Participants 5-11 Years of Age Without Evidence of SARS-CoV-2 Infection up to 1 Month After Primary Series, Evaluable Immunogenicity Population[b]

Assay Target	Time Point	BNT162b2 10 µg N=34 GMT (95% CI)	Placebo N=4 GMT (95% CI)
Reference strain	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	365.3 (279.0, 478.4)	10.0 (10.0, 10.0)
Delta variant	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
	1 month post-Dose 2	294.0 (214.6, 405.3)	10.0 (10.0, 10.0)

a. SARS-CoV-2 plaque reduction neutralization assay, SARS-CoV-2 strains: recombinant USA_WA1/2020 (reference), B.1.617.2 (Delta).
b. N = number of participants with valid and determinate assay results for the specified assays at the given dose/sampling time point. Participants with no serological or virological evidence of SARS-CoV-2 infection: defined as N-binding ant body [serum] negative from pre-Dose 1 to 1 month post-Dose 2, SARS-CoV-2 not detected by NAAT [nasal swab] prior to Dose 1 and Dose 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to 1-month post-Dose 2, and no medical history of COVID-19.

7.6 Efficacy results

Pfizer submitted supplemental, descriptive efficacy data for Phase 2/3 Cohort 1 participants 5-11 years of age, based on a total of 19 confirmed symptomatic COVID-19 cases occurring at least 7 days post-Dose 2, accrued up to the data cut-off of October 8, 2021. The evaluable efficacy population included 1,450 participants randomized to BNT162b2 and 736 participants randomized to placebo, of whom 1305 BNT162b2 and 663 placebo participants did not have evidence of SARS-CoV-2 infection from pre-Dose 1 to 7 days after Dose 2.

In participants 5-11 years of age without evidence of SARS-CoV-2 infection prior to Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 90.7%

(95% CI: 67.7%, 98.3%), with 3 COVID-19 cases in the BNT162b2 group compared to 16 in the placebo group (2:1 randomization BNT162b2 to placebo). All cases of COVID-19 occurred in children without prior history of infection. None of these cases met the criteria for severe infection. Most of the cases occurred in July-August 2021. Comorbidities at baseline (including obesity) were present in total of 20.1% of cases. No virus sequence analyses were available to determine whether these cases were caused by the Delta variant or another variant.

7.7 Safety results

Please see the Appendix 1 for Phase 1 study results.

Overview of adverse events: Phase 2/3

In C4591007 Phase 2/3 Cohort 1, e-diary data were collected from 1,511 BNT162b2 recipients and 749 placebo recipients for reactogenicity (local and systemic reactions). Overall, injection site reactions occurring within 7 days of vaccination with BNT162b2 were common, occurring in approximately 75% of participants after either Dose 1 or Dose 2. Systemic AEs occurred in approximately 50% of BNT162b2 recipients.

No Cohort 1 participants withdrew because of AEs, and there were no deaths reported. SAEs occurred in one participant each from the BNT162b2 and placebo groups, and neither were considered by the investigator or FDA to be related to the investigational agent. Immediate unsolicited AEs were rare in this study, occurring in 0.3% or less after either Dose 1 or Dose 2. See Table 9 below.

Table 9. Safety Overview, Phase 2/3 Cohorts 1 and 2, Participants 5-11 Years, Safety Population, Study C4591007

Event	BNT162b2 10 µg n/N (%)	Placebo n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination		
Dose #1	3/1518 (0.2)	3/750 (0.4)
Dose #2	4/1515 (0.3)	2/746 (0.3)
Solicited injection site reaction within 7 days		
Dose #1	1150/1511 (76.1)	254/749 (33.9)
Dose #2	1096/1501 (73.0)	237/741 (32.0)
Solicited systemic AR within 7 days		
Dose #1	715/1511 (47.3)	334/749 (44.6)
Dose #2	771/1501 (51.4)	272/741 (36.7)
From Dose 1 through 1 month after Dose 2 (cohort 1)[a]		
Any AE	166/1518 (10.9)	69/750 (9.2)
Unsolicited non-serious AE	166/1518 (10.9)	68/750 (9.1)
From Dose 1 through 1 month after Dose 2 (cohort 2)[a]		
Any AE	115/1591 (7.2)	50/788 (6.3)
Unsolicited non-serious AE	113/1591 (7.1)	50/788 (6.3)
From Dose 1 through cut-off date[b] or participant unblinding[c]		
Withdrawal due to AEs	1/3109 (<0.1)	0/1538 (0.0)
SAE	4/3109 (0.1)	1/1538 (0.1)
Deaths	0/3109 (0.0)	0/1538 (0.0)

Note: MedDRA (v24.0) coding dictionary applied.
Note: Immediate AE refers to an AE reported in the 30-minute observation period after vaccination.
%:n/N. n = Number of participants with the specified characteristic. N = number of administered participants in the specified group; this value is the denominator for the percentage calculations.
a. For cohort 1, 95% of participants had at least 2 months follow-up. For cohort 2, 71% of participants had at least 2 weeks follow-up.
b. Oct 8, 2021 for all participants (cohort 1 and cohort 2), N=3109 is the total N for BNT162
c. Three participants (2 BNT162b2, 1 placebo) turned 12 years of age during the course of the study and eligible to received 30 µg BNT162b2 under EUA; for this reason, the participants were unblinded to their treatment assignment.

7.7.1 Immediate AEs

Among the 1,518 Cohort 1 participants who received BNT162b2 Dose 1, a total of 3 reported any immediate AE, and all were injection site pain. Following Dose 2, 4 participants experienced an immediate AE, including 1 with nausea, 1 with injection site pain, 1 with injection site erythema, and 1 with erythema (skin and subcutaneous disorder).

7.7.2 Solicited adverse reactions

Solicited local adverse reactions generally occurred more commonly after Dose 2 and included pain at the injection site (71%), redness (18.5%) and swelling (15.3%). Systemic adverse reactions also occurred more frequently after Dose 2 and included fatigue (39.4%), headache (28.0%), and muscle pain (11.7%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset.

Rates of local and systemic adverse reactions in children 5-11 years of age were generally similar to those in individuals 12 years of age or older enrolled in study C4591001, with pain at the injection site slightly lower in the 5-11 year-old group, but redness and swelling slightly higher. Systemic adverse reactions such as fever, fatigue, headache, chills, and muscle pain were generally reported less frequently and were milder in severity in the 5-11 year-old group compared to individuals 12 years of age or older.

The frequencies of local and systemic adverse reactions within 7 days after each vaccination in participants with evaluable e-diary data are summarized in Tables 10, 11, and 12 below.

Table 10. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population[a], Study C4591007

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Pain at the injection site[b]				
Any[d]	74.1	31.3	71.0	29.5
Mild	58.9	27.3	52.8	25.9
Moderate	14.9	4.0	17.8	3.5
Severe	0.3	0.0	0.3	0.0
Redness[c]				
Any[d]	14.7	5.7	18.5	5.4
Mild	9.5	4.9	9.5	4.2
Moderate	5.2	0.8	8.8	1.2
Severe	0.0	0.0	0.2	0.0

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Swelling[c]				
Any[d]	10.5	2.7	15.3	2.7
Mild	5.6	1.7	7.8	2.0
Moderate	4.8	0.9	7.5	0.7
Severe	0.1	0.0	0.0	0.0

%:n/N. n=number of participants in the specified age group with the specified reaction. N=number of participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose; the N used in the percentage calculations for redness and swelling were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.
a. Randomized participants in the specified age group who received at least 1 dose of the study intervention.
b. Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
c. Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
d. Any local reaction: any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Table 11. Frequency of Solicited Systemic Reactions Within 7 Days After Dose 2 by Severity, Phase 2/3 Cohort 1 Participants 5-11 Years of Age, Safety Population, Study C4501007

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
Fever				
≥38.0°C	2.5	1.3	6.5	1.2
≥38.0°C to 38.4°C	1.5	0.5	3.4	0.7
>38.4°C to 38.9°C	0.8	0.7	2.5	0.4
>38.9°C to 40.0°C	0.2	0.1	0.5	0.1
>40.0°C	0.0	0.0	0.1	0.0
Fatigue[b]				
Any[e]	33.6	31.3	39.4	24.3
Mild	22.0	20.1	21.4	13.0
Moderate	11.3	11.1	17.3	11.2
Severe	0.3	0.1	0.7	0.1
Headache[b]				
Any[e]	22.4	24.1	28.0	18.6
Mild	16.5	17.5	18.7	12.6
Moderate	5.8	6.0	9.1	6.1
Severe	0.1	0.5	0.2	0.0
Chills[b]				
Any[e]	4.6	4.7	9.8	4.3
Mild	3.6	4.0	7.0	3.2
Moderate	1.1	0.7	2.7	0.9
Severe	0.0	0.0	0.1	0.1
Vomiting[c]				
Any[e]	2.2	1.5	1.9	0.8
Mild	1.7	1.5	1.8	0.8
Moderate	0.5	0.0	0.1	0.0
Severe	0.0	0.0	0.0	0.0
Diarrhea[d]				
Any[e]	5.9	4.1	5.3	4.7
Mild	5.2	4.1	4.8	4.3
Moderate	0.7	0.0	0.5	0.4
Severe	0.0	0.0	0.0	0.0

Event	BNT162b2 10µg Dose 1 N=1,511 %	Placebo Dose 1 N=748 %	BNT162b2 10µg Dose 2 N=1,501 %	Placebo Dose 2 N=740 %
New or worsened muscle pain[b]				
Any[e]	9.1	6.8	11.7	7.4
Mild	6.4	4.7	7.7	5.1
Moderate	2.6	2.1	3.9	2.3
Severe	0.1	0.0	0.1	0.0
New or worsened joint pain[b]				
Any[e]	3.3	5.5	5.2	3.6
Mild	2.3	4.1	3.8	2.7
Moderate	1.1	1.3	1.4	0.9
Severe	0.0	0.0	0.0	0.0
Use of antipyretic or pain medication[f]	14.4	8.3	19.7	8.1

%: n/N. n = Number of participants with the specified reaction. N = Number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose; the N used in the percentage calculations for fever and use of antipyretic or pain medication were 749 after Dose 1 and 741 after Dose 2 in the placebo group, due to an e-diary error.
a. All participants in the specified age group who received at least 1 dose of the study intervention.
b. Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.
c. Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.
d. Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.
e. Any systemic event: any fever ≥38.0℃, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
f. Severity was not collected for use of antipyretic or pain medication.

Table 12. Characteristics of Solicited Local and Systemic Adverse Reactions, Phase 2/3 Cohort 1, Participants 5-11 Years, Safety Population, Vaccine Group as Administered, Study C4591007

Event	BNT162b2 10 µg Dose 1 n[a]/N[b]	Placebo Dose 1 n[a]/N[b]	BNT162b2 10 µg Dose 2 n[a]/N[b]	Placebo Dose 2 n[a]/N[b]
Any solicited local reaction				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.0 (1, 12)
Persisted beyond 7 days	11/1511	9/749	8/1501	5/741
Redness				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 5)	2.0 (1, 6)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 8)	2.0 (1, 10)	1.0 (1, 11)
Persisted beyond 7 days	4/1511	1/749	2/1501	1/741
Swelling				
Day of onset: median (min, max)	2.0 (1, 4)	1.0 (1, 7)	2.0 (1, 4)	1.0 (1, 5)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 9)	2.0 (1, 10)	1.0 (1, 12)
Persisted beyond 7 days	1/1511	1/749	2/1501	2/741
Pain at injection site				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.5 (1, 12)
Persisted beyond 7 days	7/1511	8/748	6/1501	5/740
Any solicited systemic reaction				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 10)
Persisted beyond 7 days	29/1511	15/749	30/1501	13/741

	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
Fever				
Day of onset: median (min, max)	2.0 (2, 7)	2.5 (1, 7)	2.0 (1, 7)	6.0 (2, 7)
Duration: median (min, max)	1.0 (1, 3)	1.0 (1, 3)	1.0 (1, 5)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Fatigue				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 21)	2.0 (1, 9)	1.0 (1, 14)	1.0 (1, 10)
Persisted beyond 7 days	16/1511	7/748	17/1501	6/740
Headache				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 9)
Persisted beyond 7 days	12/1511	9/748	10/1501	6/740
Chills				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 10)	1.0 (1, 7)	1.0 (1, 8)	1.0 (1, 8)
Persisted beyond 7 days	3/1511	0	1/1501	1/740
Vomiting				
Day of onset: median (min, max)	4.0 (1, 7)	4.0 (1, 6)	2.0 (1, 6)	3.0 (2, 6)
Duration: median (min, max)	1.0 (1, 5)	1.0 (1, 1)	1.0 (1, 2)	1.0 (1, 5)
Persisted beyond 7 days	0	0	0	0
Diarrhea				
Day of onset: median (min, max)	3.0 (1, 7)	3.0 (1, 7)	3.0 (1, 7)	4.0 (1, 7)
Duration: median (min, max)	1.0 (1, 8)	1.0 (1, 6)	1.0 (1, 28)	1.0 (1, 9)
Persisted beyond 7 days	1/1511	0	2/1501	2/740
New or worsened joint pain				
Day of onset: median (min, max)	2.0 (1, 6)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 7)	1.0 (1, 4)	1.0 (1, 18)	1.0 (1, 6)
Persisted beyond 7 days	0	0	1/1501	0
New or worsened muscle pain				
Day of onset: median (min, max)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 9)	1.0 (1, 8)	1.0 (1, 9)	1.0 (1, 6)
Persisted beyond 7 days	1/1511	1/748	3/1501	0

a. n = Number of participants with the specified reaction persisted beyond 7 days.
b. N = number of participants reporting at least 1 yes or no response for the specified reaction after the specified dose.

7.7.3 Subgroup analyses of solicited adverse reactions

Subgroup analyses were performed for solicited adverse reactions, comparing BNT162b2 and placebo groups by sex, race, ethnicity, and baseline SARS-CoV-2 status at baseline. No notable differences were observed among the study groups, although certain subgroups such as Black or African American race and Hispanic/Latino ethnicity had too few participants to draw meaningful conclusions.

7.7.4 Unsolicited adverse events

In 1 group of participants (cohort 1; initial enrollment cohort), non-serious adverse events from Dose 1 through up to 30 days after Dose 2 up to the cut-off date of September 06, 2021, in ongoing follow up were reported by 10.9% of Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) recipients and by 9.1% of placebo recipients. In this group of participants, >99% had follow-up 30 days post Dose 2. In a second group of participants (cohort 2; expansion cohort) for which the median follow-up was 2.4 weeks (range 0 – 3.7 weeks), non-serious adverse

events from Dose 1 through the cut-off date of October 8, 2021, were reported by 7.1% of Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) recipients and by 6.3% of placebo recipients.

In the initial enrollment cohort, from Dose 1 through 30 days after Dose 2, lymphadenopathy was reported in 13 (0.9%) participants in the Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) group vs. 1 (0.1%) in the placebo group. In the expansion cohort, from Dose 1 through the cut-off date, lymphadenopathy was reported in 6 (0.4%) participants in the Pfizer BioNTech COVID-19 Vaccine (10 mcg modRNA) group vs. 3 (0.4%) in the placebo group. There were no other notable patterns between treatment groups for specific categories of non-serious adverse events that would suggest a causal relationship to Pfizer BioNTech COVID 19 Vaccine.

7.7.5 SAEs

In Cohort 1 (median of 2.3 months follow-up post Dose 2), SAEs occurred at frequency of 0.1% in both BNT162b2 and placebo recipients. For BNT162b2 recipients, only one SAE was reported, an upper limb fracture. In Cohort 2 (median of 2.4 weeks follow-up post Dose 2), 3 BNT162b2 recipients (0.2%) reported a SAE: 1 infection of the knee, 1 foreign body ingestion, and 1 epiphyseal fracture. All SAEs reported in the study were considered by the study investigator to be unrelated to vaccination. FDA agrees with this assessment.

Deaths: No deaths have occurred during the study in either Cohort 1 or 2.

7.7.6 AEs of clinical interest

FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs among recipients 5-11 years of age in study C4591007 Phase 2/3 Cohort 1 through the September 6, 2021, cut-off date. SMQs (narrow and broad in scope) were conducted on AE Preferred Terms (PTs) that could represent various conditions, including but not limited to angioedema, arthritis, cardiomyopathy, ischaemic heart disease, cardiac arrhythmia, cardiac failure, central nervous system vascular disorders, convulsions, demyelination, embolic and thrombotic events, hearing and vestibular disorders, hematopoietic cytopenias, hypersensitivity, peripheral neuropathy, thrombophlebitis, and vasculitis. For example, the cardiomyopathy SMQ includes PTs that may be related to myocarditis and pericarditis, such as chest pain, palpitations, dyspnea, syncope, troponin elevation, ECG with ST elevation or PR depression, pericardiac rub, or echocardiographic findings.

For Cohort 1, the SMQ analyses resulted in identification of 19 participants with AEs of interest in the SMQs (narrow and broad in scope) in the BNT162b2 group and 6 in the placebo group. The SMQ analyses revealed an imbalance of AEs potentially representing allergic reactions, with 14 participants in the vaccine group (0.92%) reporting hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) compared with 4 participants in the placebo group (0.53%).

For Cohort 2, the SMQ analyses with respect to hypersensitivity identified 9 participants in the vaccine group (0.57%) and 4 in the placebo group (0.51%) reporting unsolicited AEs in this category, primarily skin and subcutaneous disorders of rash and dermatitis. The SMQ for angioedema was reported in 3 (0.19%) in the vaccine group compared to 1 (0.13%) in the placebo group. These events included one participant with both angioedema and urticaria, and 3 participants with urticaria.

One participant, a 6-year-old female in the BNT162b2 group, had a non-serious AE of Henoch-Schönlein purpura which was diagnosed 21 days after Dose 1 and was considered non-serious.

No new or unexpected adverse reactions were identified based on these SMQ results.

In Cohorts 1 and 2, “chest pain” was reported in a total of 12 participants: 6 assigned to the BNT162b2 group and 6 assigned to placebo. Chest pain resolved in all participants within 1-2 days of onset. No participants required a cardiac evaluation or ER visit, and none were hospitalized. In each case the AE was considered to be noncardiac in origin.

7.7.7 AEs leading to study withdrawal

In C4591007 Phase 2/3 Cohort 1, there were no AEs leading to withdrawal. In Cohort 2 with a follow up cut-off of October 8, 2021, 1 participant was withdrawn due to AEs of fever 2 days after Dose 1 and worsening of neutropenia (previously diagnosed as benign transient neutropenia. Dose 2 was not administered.

7.8 Study C4591007 Phase 2/3 summary

This EUA request included safety data from 1,518 BNT162b2 recipients and 750 placebo (saline) recipients 5-11 years of age in the Phase 2/3 portion (Cohort 1) of an ongoing clinical trial, C4591007; Among Cohort 1 participants, 95.1% had safety follow up ≥2 months after Dose 2 at the time of the September 6, 2021, data cut-off. Safety data from an additional 1,591 BNT162b2 recipients and 788 placebo recipients from the Phase 2/3 portion of the trial (Cohort 2) were provided for assessment of SAEs and other AEs of interest (e.g., myocarditis, pericarditis, anaphylaxis); the median duration of follow-up was 2.4 weeks post-Dose 2 at the time of the October 8, 2021, data cut-off for Cohort 2.

Immunobridging success criteria were met for geometric mean neutralizing antibody titers and seroresponse rates at 1 month post-Dose 2 against the USA_WA1/2020 reference strain, as assessed by 50% mNG microneutralization assay, among children 5-11 years of age in study C4591007 Cohort 1 compared to study participants 16-25 years of age randomly selected from study C4591001. Subgroup immunogenicity analyses by age, gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions. Descriptive immunogenicity analyses, based on 50% plaque reduction neutralization test (PRNT), showed that a 10 µg BNT162b2 primary series elicited PRNT neutralizing titers against the reference strain and B.1.617.2 (Delta) strain in participants 5-11 years of age (34 BNT162b2, 4 placebo). Lastly, in a supplemental descriptive efficacy analysis, VE against symptomatic COVID-19 after 7 days post-Dose 2 as of the October 8, 2021, data cut-off was 90.7% (2-sided 95% CI: 67.7%, 98.3%) in participants 5-11 years of age without prior evidence of SARS-CoV-2 infection; 3 cases of COVID-19 occurred in the BNT162b2 group and 16 in the placebo group. All cases of COVID-19 occurred in participants 5-11 years of age without prior history of SARS-CoV-2 infection, and most occurred during July-August 2021. At the time of data cut-off, no cases met the criteria for severe COVID-19 infection.

Solicited local and systemic ARs generally occurred more frequently after Dose 2, and the most commonly reported solicited ARs were pain at the injection site (71%), fatigue (39.4%), and headache (28%). Most local and systemic reactions were mild to moderate in severity, with median onset 2 days post-vaccination, and resolved within 1 to 2 days after onset. The most frequently reported unsolicited adverse event (AE) in Cohort 1, lymphadenopathy was reported

in 13 BNT162b2 recipients (0.9%); in Cohort 2, lymphadenopathy was reported in 6 BNT162b2 recipients (0.4%). In Cohort 1, more BNT162b2 recipients (n=14; 0.92%) reported hypersensitivity-related AEs (primarily skin and subcutaneous disorder including rash and dermatitis) than placebo recipients (n=4; 0.53%). For Cohort 2, hypersensitivity reactions were reported in 9 participants (0.6%) in the BNT162b2 group; events included a Type IV hypersensitivity reaction and other rashes. Overall, from the combined safety database of 3,109 BNT162b2 participants, 4 BNT162b2 participants reported a SAE, and all of the SAEs were considered unrelated to vaccination. One BNT162b2 recipient withdrew from the study due to fever (40.1ºC) that occurred 2 days after Dose 1 and neutropenia that had worsened from baseline; the neutropenia was related to a pre-existing condition. There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths. Subgroup safety analyses by gender, race and ethnicity, obesity and baseline SARS-CoV-2 status showed no notable differences compared to the overall study population, although some subgroups were too small to draw meaningful conclusions.

8 FDA REVIEW OF OTHER INFORMATION SUBMITTED

8.1 Chemistry, Manufacturing, and Control (CMC) information

The currently authorized/approved Pfizer-BioNTech COVID-19 vaccine, mRNA (BNT162b2), is formulated in phosphate-buffer saline (PBS) containing sodium chloride and potassium chloride (referred to as PBS/Sucrose formulation), and this formulation was used in Study C4591007. To provide a vaccine with an improved stability profile and greater ease of use at vaccine distribution sites, Pfizer/BioNTech have developed a new drug product (DP) formulation using tromethamine (Tris) buffer (referred to as Tris/Sucrose formulation). The new formulation no longer contains sodium chloride and potassium chloride. The BNT162b2 Tris/Sucrose vaccine product is formulated at 0.1 mg/mL of mRNA in 10 mM Tris, 300 mM sucrose, pH 7.4. For use in children 5-11 years of age, the Tris/Sucrose DP is filled at 1.3 mL fill volume in glass vials and requires dilution with 1.3 mL 0.9% sodium chloride for injection prior to administration. After dilution, each vial provides a total of 10 doses of 10-µg mRNA, each in 0.2 mL injection volume.

The Tris/Sucrose DP is currently manufactured using facilities already authorized or approved for the manufacture of the PBS/Sucrose DP. The manufacturing process for the Tris/Sucrose DP uses the same drug substance (DS) and the same lipids and has the same initial steps as for the current PBS/Sucrose formulation, including the steps of (b) (4) and (b) (4) Changes are implemented in the formulation buffer (from PBS to Tris) during the (b) (4) DP formulation unit operations. Subsequent steps of sterile filtration, aseptic filling, labeling and freezing for storage are essentially the same between the two formulations with only adjustments to reflect the different fill volumes. The Tris/Sucrose DP manufacturing process was validated by process-performance qualification (PPQ) execution, including production of 3 PPQ lots filled at 2.25 mL, supporting the 30-µg mRNA dose, and two PPQ lots filled at 1.3 mL, supporting the 10-µg mRNA dose. The validation results demonstrated that with a well-defined process protocol, consistent manufacturing of the BNT162b2 Tris/Sucrose DP can be achieved for both fill volumes.

Analytical comparability was demonstrated for the Tris/Sucrose DP when compared with the currently authorized/approved PBS/sucrose DP based on in-process test results, final DP release test results and characterization test results. Analytical comparability uses laboratory testing to demonstrate that a change in product formulation does not impact a product's safety or effectiveness. In the case of a lipid nanoparticle containing mRNA such as BNT162b2 multiple different release parameters are evaluated, ranging from product appearance to size of

the lipid-nanoparticle to the integrity of the mRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine

In this case, analytical comparability to the current PBS/Sucrose formulation was demonstrated for the Tris/Sucrose DP through a combination of release and characterization testing. Comparability was established for the three PPQ Tris/Sucrose DP lots manufactured at production scale and filled at a volume of 2.25 mL.

The manufacturing specifications for the Tris/Sucrose DP are based on those established for the authorized/approved PBS/Sucrose DP and are not affected by the change from the PBS/Sucrose to the Tris/Sucrose buffer. The analytical procedures for Tris/Sucrose DP release and stability testing are identical to the corresponding PBS/Sucrose procedures with the exception of an update to include minor modifications in sample preparations to account for the difference in mRNA concentration between the two formulations. Validation of each assay method for the Tris/Sucrose DP was performed and the validation results have demonstrated that all the analytical procedures are suitable for their intended use.

Based on the available stability data for the Tris/Sucrose DP and the established 9-month expiry for the PBS/Sucrose DP, the initial shelf-life for the BNT162b2 Tris/Sucrose vaccine product is 6 months when stored frozen between -90°C to -60°C. The available stability data also support storage at 2-8°C for up to 10 weeks once the frozen Tris/Sucrose vaccine has been thawed. At the vaccine administration sites, the 10 µg Tris/Sucrose DP vials can be stored at 2°C to 25°C for up to 24 hours. However, after the first puncture, the vaccines must be used within 12 hours. This proposed in-use shelf-life is supported by compatibility assessment and microbial in-use challenge studies.

Taken together, the analytical comparability assessment demonstrated that the Tris/Sucrose DP lots are comparable to the previously authorized/approved BNT162b2 PBS/Sucrose DP. The results further support the capability of the commercial manufacturing process to produce a consistent Tris/Sucrose DP with acceptable quality.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine is performed at a number of facilities. For each of these facilities, FDA requested and reviewed information on equipment, facilities, quality systems and controls, container closure systems as well as other information as per the guidance, “Emergency Use Authorization for Vaccines to Prevent COVID-19, February 2021”, to ensure that there is adequate control of the manufacturing processes and facilities.

In particular, the following information was assessed:

- Facilities appear to be adequately designed and maintained and manufacturing process, personnel, air direction and waste flow are suitable for manufacturing.
- Multiple product manufacturing areas and equipment used to manufacture the COVID-19 vaccine were assessed and cleaning and changeover procedures were evaluated and appear adequate. Cross-contamination controls appear suitable to mitigate risk of cross contamination.
- The successful qualification of critical equipment for drug substance and drug product manufacturing was verified.
- Aseptic process information and validation studies were assessed and appear acceptable.

- Drug product solution sterilization by filtration was reviewed and appears acceptable.
- Sterilization and depyrogenation of pertinent equipment and materials, including container/closure components, description and validation studies appear acceptable.
- Utilities qualification studies including HVAC systems, appear adequate. Air cleanliness of the manufacturing cleanrooms were adequately controlled and maintained.
- Container/closure integrity studies to ensure sterility of drug product in the final container were conducted and appear adequate.

FDA also performed inspections at two facilities, reviewed the inspectional histories of all applicable facilities and all available information to ascertain whether each facility meets current good manufacturing practice requirements. We find that all the facilities are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine under EUA for individuals five years of age and older.

8.2 Pharmacovigilance activities

Pfizer submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with BNT162b2 in individuals 5-11 years of age. The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

Pfizer-BioNTech plans to conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine, including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); COVID-19 disease resulting in hospitalization or death; multisystem inflammatory syndrome (MIS)
- Adverse event reporting in accordance with regulatory requirements for the licensed vaccine, COMIRNATY
- Additionally, following approval of COMIRNATY, the Sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies, that would be modified to encompass the evaluation of children 5-11 years of age include active surveillance safety studies using large health insurance claims and/or electronic health record database(s):

  – Study C4591009: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States

    Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general U.S. population of all ages, pregnant women, the immunocompromised, and persons with a prior history of COVID-19 within selected data sources participating in the U.S. Sentinel System.

- Study C4591021: Post-conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

  Objective: To assess the potential increased risk of events of interest, including myocarditis/pericarditis, after being vaccinated with at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.

- Study C4591021 Substudy: Substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

  Objective: To describe the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within one year of myocarditis/pericarditis diagnosis among individuals vaccinated with BNT162b2 as well as individuals not vaccinated with a COVID-19 vaccine.

- Study C4591036: Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network [PHN]). Working title: *Myocarditis/pericarditis follow-up study within the Pediatric Heart Network*

  Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.

Pfizer-BioNTech also plans to include vaccine effectiveness analyses among individuals 5-11 years of age in Study C4591014 entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California.”

8.3 Clinical assay information

The SARS-CoV-2 mNG microneutralization assay used in the Phase 2/3 clinical study C4591007 measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for neutralizing antibody assessment against the USA_WA1/2020 strain.

Additionally, a plaque reduction neutralization test (PRNT) was used to determine neutralizing titers against the reference USA_WA1/2020 strain and the SARS-CoV-2 virus Delta variant (a recombinant virus with Delta variant spike gene on the USA_WA1/2020 genetic background). The PRNT is a non-validated assay and was used for exploratory purposes only.

8.4 Inspection of clinical study sites

The review team decided that Bioresearch Monitoring (BIMO) inspections are not needed to support the review of this EUA amendment. Sites under this study had been previously inspected.

8.5 EUA prescribing information and fact sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

For the Fact Sheets applicable for the 12 years and older population, certain information has been updated to reflect changes made to the scope of the October 29, 2021 authorization. For example, certain portions of the fact sheets have been revised to: refer to the use of different color caps; identify the availability of the new formulation; clarify the new age groups for whom the vaccine is authorized; and explain which dosage may be used for individuals who receive their first dose at age 11 and turn 12 years old before their second dose. In addition, we made additional changes to address the potential that the previous versions of the fact sheets created confusion. For example, we removed a sentence from the fact sheets stating that COMIRNATY and the Pfizer-BioNTech COVID-19 Vaccine are "legally distinct with certain differences that do not impact safety or effectiveness." Communicating the legal relationship of the different products did not appear relevant to the target audience of these fact sheets, as the more relevant information for them is that when prepared according to their respective instructions for use, the FDA-approved COMIRNATY and the two EUA-authorized formulations of Pfizer-BioNTech COVID-19 Vaccine for ages 12 years of age and older can be used interchangeably without presenting any safety or effectiveness concerns. We continue to explain in the Letter of Authorization that the original formulation of the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY are legally distinct with certain differences that do not impact safety or effectiveness.

9 BENEFIT/RISK IN THE CONTEXT OF THE PROPOSED EUA FOR PFIZER-BIONTECH COVID-19 VACCINE IN CHILDREN 5-11 YEARS OF AGE

9.1 Known and potential benefits

Available data support the effectiveness of the Pfizer-BioNTech COVID-19 Vaccine in preventing symptomatic COVID-19 among children 5-11 years of age. The immunobridging analyses from study C4591007 met pre-specified success criteria that allow for inference of vaccine effectiveness in this age group. Furthermore, direct evidence for clinical benefit is provided by a preliminary descriptive analysis of VE against symptomatic COVID-19 of any severity, with a VE point estimate of 90.7% (2-sided 95% CI: 67.7%, 98.3%) compared with placebo. This VE point estimate is similar to the estimated VE among adults in enrolled in the Phase 3 placebo-controlled efficacy trial that supported the original EUA authorization as well as VE estimates in adults from real-world observational studies. While no cases of severe COVID-19 were accrued during study follow-up to date, it is highly likely that vaccine effectiveness against severe COVID-19 among children 5-11 years of age will be even higher than vaccine effectiveness against non-severe COVID-19, as is the case in adults. Prevention of symptomatic COVID-19 will also likely result in prevention of sequelae such as post-COVID symptoms (also known as "long COVID") and MIS-C. Since the overall burden of COVID-19 is lower in children 5-11 years of age compared with adults, the individual-level and population-level benefits of the vaccine, in particular among healthy vaccine recipients at low risk of severe COVID-19, are expected to be lower in children 5-11 years of age than in adults and will depend largely on the incidence of COVID-19 (see Section 9.5). Nonetheless, given the uncertainty of the COVID-19 pandemic and likelihood of continued SARS-CoV-2 transmission during over the ensuing

months, widespread deployment of the vaccine for use among children 5-11 years of age will likely have a substantial effect on COVID-19 associated morbidity and mortality in this age group. The impact of measures currently in place to mitigate against SARS-CoV-2 transmission in settings where children congregate with other children and with adults also contributes to consideration of vaccine benefits in this age group. If these measures were relaxed, the potential benefits of vaccination in this age group would be even greater.

9.2 Data gaps related to benefits

The data gaps associated with benefits of the Pfizer-BioNTech COVID-19 vaccine when used in children 5-11 years of age include the following:

- Duration of protection and potential need for booster doses.
- Effectiveness in certain populations at high risk of severe COVID-19, including highly immunocompromised children.
- Benefits (and in particular the need for a 2-dose primary series) in children previously infected with SARS-CoV-2 relative to those who have not been previously infected; despite these uncertainties, however, available data support that previously infected individuals are susceptible to re-infection.
- Future vaccine effectiveness as influenced by characteristics of the pandemic, including emergence of new variants.
- Vaccine effectiveness against asymptomatic infection.
- Vaccine effectiveness against transmission of SARS-CoV-2.

9.3 Known and potential risks

In children 5-11 years of age, there were higher rates of solicited local and systemic adverse reactions, lymphadenopathy, and hypersensitivity reactions in vaccine recipients than placebo recipients. Overall, the rates of these adverse reactions reported among children 5-11 years of age were lower than those reported among older age groups and likely reflect the lower vaccine mRNA content evaluated in children 5-11 years of age. In considering unsolicited adverse events reported among children 5-11 years of age, the available safety data from a total database of over 3,000 vaccine recipients do not suggest any new safety concerns compared with the safety profile described in older age groups.

Anaphylaxis, primarily among individuals with a history of severe allergic reactions to other medications or foods, has been documented to occur at a rate of approximately 6 cases per million doses among vaccine recipients 16 years of age and older (similar in magnitude to reported rates of anaphylaxis following licensed preventive vaccines). Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the pharmacovigilance plan for the vaccine.

Myocarditis/pericarditis, in particular in the first week following Dose 2, is a known risk associated with the Pfizer-BioNTech COVID-19 Vaccine and is greatest among adolescent males 16-17 years of age compared with both younger and older age groups. In contrast to myocarditis in the pre-COVID era, most reported cases of vaccine-associated myocarditis have involved rapid resolution of symptoms with conservative management; however, the long-term sequelae of vaccine-associated myocarditis, if any, remain to be determined. The risk of vaccine associated myocarditis/pericarditis among children 5-11 years of age is unknown at this time.

No cases of myocarditis or pericarditis were reported among over 3,000 vaccine recipients in the clinical trial, most of whom had at least 2 weeks of follow-up post-Dose 2. However, this safety database is not large enough to quantify the frequency of this uncommon adverse reaction. Data supporting that the risk of vaccine-associated myocarditis may be lower among children 5-11 years of age compared with adolescents 16-17 years of age include a lower rate of vaccine-associated myocarditis among adolescents 12-15 years of age compared with adolescents 16-17 years of age, a lower incidence of myocarditis in the pre-COVID era among children 5-11 years of age compared with adolescents, and lower rates of systemic reactogenicity in children 5-11 years of age associated with the lower vaccine mRNA content intended for use in this age group.

9.4 Data gaps related to risks

The data gaps associated with risks of the Pfizer-BioNTech COVID-19 vaccine when used in children 5-11 years of age include the following:

- Risk of myocarditis/pericarditis, as described in detail in Section 9.3 above.
- Safety in certain subpopulations: available data are insufficient to make conclusions about the safety of the vaccine in certain subpopulations such as immunocompromised children. Safety data in children previously infected with SARS-CoV-2 are limited; however, available data do not suggest increased reactogenicity or other safety concerns among previously infected children.
- Adverse reactions that are very uncommon or that require longer follow-up to be detected. Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

9.5 Quantitative benefit-risk assessment for children 5-11 years of age

FDA conducted a quantitative benefit-risk assessment for use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5-11 years of age. The key benefits assessed include preventable COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths due to COVID-19. The key risks include excess myocarditis/pericarditis cases, and related hospitalizations, ICU admissions, and deaths attributable to myocarditis/pericarditis. The benefits and risks are assessed per million fully vaccinated individuals with and without stratification by sex, and with comparison to age groups 12-15 years and 16-17 years.

The model assesses the benefits of vaccine protection in a 6-month period after completion of the primary series. The model assumes VE of 70% against COVID-19 cases and 80% against COVID-19 associated hospitalization based on a CDC vaccine effectiveness study for ages 20+ years during circulation of the Delta variant.[48] The incidence rates of COVID-19 cases for the week of September 11, 2021, are obtained from COVID-NET for all sex/age groups. COVID-NET covers approximately 10 percent of the U.S. population. Four-week averages of incidence rate for hospitalizations (week ending on 8/21/2021 to week ending on 9/11/2021) are used due to the variability in rates given the small numbers of hospitalizations per age/sex group. Estimates for the percentage of hospitalizations resulting in ICU admission and the percentage of hospitalized patients who die are based on cumulative rates of hospitalizations, ICU admissions, and deaths for each sex/age groups reported in COVID-NET since March 2020. The death rate among 5-11 year-olds is lower in COVID-NET than in other national data sources such as the CDC COVID-19 Data Tracker. This could be due to geographic differences in case reporting and the recent trajectory of the pandemic. This difference will lead to a conservative estimate of benefits in the model. The model assumes that incidence rates of COVID-19 cases and hospitalizations remain constant over the assessment period of 6 months.

The estimates for excess myocarditis/pericarditis among fully vaccinated individuals ages 12-15 years and ages 16-17 years are based on Optum healthcare claims data for the period 12/10/2020 to 07/10/2021, which is a conservative approach that includes non-confirmed cases. For this analysis the estimate for ages 12-15 years is applied to ages 5-11 years because vaccine-associated myocarditis/pericarditis data are not available for this age group. The proportions of vaccine-attributable myocarditis/pericarditis hospitalizations and ICU admissions are obtained from Vaccine Safety Datalink (12-17 year-old group[49]). Some of these hospitalizations and ICU admissions may be precautionary and therefore not clinically equivalent to COVID-19 hospitalizations and ICU admissions. The dose intended for use in children 5-11 years of age (10 µg), is lower than the dose used under EUA in adolescents 12-15 years of age (30 µg), and the observed systemic reactogenicity associated with the respective antigen contents in clinical trials is lower for children 5-11 years of age as well. Thus, assuming the same rate of vaccine-associated myocarditis for children 5-11 years of age as has been observed for adolescents 12-15 years of age in Optum claims data may be a conservative overestimate.

The model inputs described above were used to develop “Scenario 1,” a base model from which five alternative scenarios were derived to address key uncertainties associated with model inputs. The model’s results indicate that the incidence of COVID-19 is highly influential to the benefits of the vaccine. To account for uncertain dynamics of the pandemic, FDA assesses the benefits and risks under Scenario 2 with COVID-19 incidence close to recent peak, and Scenario 3 with COVID-19 incidence close to the lowest recorded incidence since the beginning of the pandemic. These two scenarios provide likely bounds for potential future states of the pandemic. Scenario 4 (90% vaccine efficacy against cases and 100% efficacy against hospitalizations) tests the impact on benefits and risks of potentially higher vaccine efficacy suggested by the Sponsor’s newly submitted descriptive efficacy analysis (see Section 7.6). Scenario 5 with a 3x multiple of the death rate is used to match the cumulative death rate for 5-11 year-olds seen in CDC Data Tracker. Scenario 6 uses a 50% lower rate of attributable myocarditis than Scenario 1 to address the uncertainty associated with the rate of vaccine-attributable myocarditis in children 5-11 years, for whom the data is not available.

The results of the benefit-risk assessment are summarized in Table 13 below. The results predict that under Scenarios 1 (base), 2 (peak COVID incidence), 4 (high efficacy), and 5 (high COVID death rate), and 6 (low attributable myocarditis rate) the benefits of the Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series outweigh the risks for ages 5-11 years. Under Scenario 3 (low incidence), the model predicts more excess hospitalizations due to vaccine-related myocarditis/pericarditis compared to prevented hospitalizations due to COVID-19 in males and in both sexes combined. However, in consideration of the different clinical implications of hospitalization for COVID-19 versus hospitalization for vaccine-associated myocarditis/pericarditis, and benefits related to prevention of non-hospitalized cases of COVID-19 with significant morbidity, the overall benefits of the vaccine may still outweigh the risks under this low incidence scenario. If the myocarditis/pericarditis risk in this age group is lower than the conservative assumption used in the model, the benefit-risk balance would be even more favorable.

Table 13. Model-Predicted Benefit-Risk Outcomes of Scenarios 1-6 per One Million Fully Vaccinated Children 5-11 Years Old

Sex	**Benefit**: Prevented COVID-19 Cases	**Benefit**: Prevented COVID-19 Hospitaliza-tions	**Benefit**: Prevented COVID-19 ICU Admissions	**Benefit**: Prevented COVID-19 Deaths	**Risk**: Excess Myocarditis Cases	**Risk**: Excess Myocarditis Hospitaliza-tions	**Risk**: Excess Myocarditis ICU Admissions	**Risk**: Excess Myocarditis Deaths
Males & Females								
Scenario 1	45,773	192	62	1	106	92	34	0
Scenario 2	54,345	250	80	1	106	92	34	0
Scenario 3	2,639	21	7	0	106	92	34	0
Scenario 4	58,851	241	77	1	106	92	34	0
Scenario 5	45,773	192	62	3	106	92	34	0
Scenario 6	45,773	192	62	1	53	46	17	0
Males only								
Scenario 1	44,790	203	67	1	179	156	57	0
Scenario 2	54,345	250	82	1	179	156	57	0
Scenario 3	2,639	21	7	0	179	156	57	0
Scenario 4	57,857	254	83	1	179	156	57	0
Scenario 5	44,790	203	67	3	179	156	57	0
Scenario 6	44,790	203	67	1	89	78	29	0
Females only								
Scenario 1	45,063	172	54	1	32	28	10	0
Scenario 2	54,345	250	78	2	32	28	10	0
Scenario 3	2,639	21	7	0	32	28	10	0
Scenario 4	57,938	215	67	2	32	28	10	0
Scenario 5	45,063	172	54	4	32	28	10	0
Scenario 6	45,063	172	54	1	16	14	5	0

Scenario 1: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 2: COVID-19 incidence at peak of U.S. Delta variant surge at end of August 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 3: COVID-19 incidence as of nadir in June 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization.
Scenario 4: COVID-19 incidence as of September 11, 2021, VE 90% vs. COVID-19 cases and 100% vs. COVID-19 hospitalization.
Scenario 5: COVID-19 case incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19. hospitalization, COVID-19 death rate 300% that of Scenario 1.
Scenario 6: COVID-19 incidence as of September 11, 2021, VE 70% vs. COVID-19 cases and 80% vs. COVID-19 hospitalization, excess myocarditis cases 50% of Scenario 1.

10 VRBPAC SUMMARY

The 170th meeting of the VRBPAC was held on October 26, 2021, to discuss the data submitted by Pfizer in support of the EUA amendment request and other data to inform benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine in children 5-11 years of age. In addition to presentations from the Center for Disease Control and Prevention on the epidemiology of COVID-19 in children and on known safety signals, Pfizer and the FDA presented data from Study C4591007, and the FDA also presented a benefit-risk analysis modeling use of the vaccine in the intended population. The Committee's discussion focused on the benefits and risks of the vaccine, and associated uncertainties, taking into account the current trend of the pandemic. There was concern expressed that some populations, such as those with comorbidities, might benefit more from the vaccine than healthy children who are generally at low risk of serious complications of COVID-19, in particular those who have previously been infected with SARS-CoV-2 and may already benefit from natural immunity against currently

circulating variants. The voting question presented to the Committee was “Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age.” The vote was 17 yes, 0 no, and 1 abstain. Several of those voting yes explained that they wanted to make the option of vaccination available to this age group based on individual considerations. In explaining their votes a few of the committee members noted their concern that the vaccine might be mandated at this time, given the uncertainties around benefit and risk balance in the setting of decreasing COVID-19 incidence and increasing SARS-CoV-2 seroprevalence in this age group. FDA representatives explained that FDA does not mandate vaccines for the general public and that vaccine mandates are outside the scope of FDA's decision making process. Some members also noted the importance of safety monitoring as well as the importance of obtaining more experience with the vaccine. A few other members noted that the availability of the vaccine will help children directly and potentially help reduce transmission of SARS-CoV-2.

11 OVERALL SUMMARY AND RECOMMENDATIONS

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in Section 6 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 7 of this review, Pfizer-BioNTech COVID-19 Vaccine, when administered as a 2-dose primary series in children 5 -11 years of age, may be effective in preventing serious or life-threatening disease or condition that can be caused by SARS-CoV-2. Vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralizing antibody titers at one month after dose 2 in participants 5-11 years of age with those of young adults 16 to 25 years of age, the most clinically relevant subgroup of the study population in whom VE has been demonstrated. In the planned immunobridging analysis, the GMT ratio of neutralizing antibody titers (children to young adults) was 1.04% (95% CI: 0.93, 1.18) meeting the success criterion (lower bound of the 95% CI for the GMT ratio > 0.67 and the point estimate ≥1). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SAR-Co-V2 infection were seen in 99.2% percent of children and 99.2% percent of young adults, with a difference in seroconversion rates of 0 (95% CI -2.0, 2,2), meeting the prespecified success criteria of the lower limit of the 95% CI for the difference in seroresponse of greater than -10%. immunogenicity outcomes were consistent across demographic subgroups. Descriptive analyses from a randomly selected subset of participants (34 BNT162b2 recipients, 4 placebo recipients) with no evidence of infection up to 1 month post-Dose 2 demonstrated that a 10 µg primary series elicited PRNT neutralizing titers against both the reference strain and the Delta variant. In a supplemental efficacy analysis, VE after 7 days post-Dose 2 was 90.7% (95% CI: 67.7%, 98.3%); 3 cases of COVID-19 occurred in participants 5-11 years of age without prior history of SARS-CoV-2 infection, and most occurred during July-August 2021. Although based on a small number of cases and descriptive analysis, the supplemental VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

- Based on the data summarized in Section 7 and benefits and risks in Section 9 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known and potential risks include common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, chills, fever and joint pain), less commonly lymphadenopathy, and hypersensitivity reactions (e.g., rash, pruritis, urticaria, angioedema), and rarely anaphylaxis and myocarditis/pericarditis (based on experience in Pfizer-BioNTech COVID-19 vaccine recipients 12 years of age and older). Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group and surveillance for other adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up. Acknowledging the current uncertainties around benefits and risks, a quantitative analysis using conservative assumptions predicts that overall benefits of vaccination outweigh risks in children 5-11 years of age.

- COMIRNATY is the only FDA approved vaccine indicated for active immunization for prevention of COVID-19 caused by SARS-CoV-2. It is licensed as a 2-dose primary series given 3 weeks apart in individuals 16 years. The Pfizer-BioNTech COVID-19 vaccine is authorized as a 2-dose primary series given weeks apart in adolescents 12-15 years of age. A third dose is authorized for use, as part of the primary series, in immunocompromised individuals 12 years and older. A booster dose administered at least 6 months after completing a primary series is authorized for in use in individuals 65 years of age and older, individuals at high risk of severe COVID-19, and individuals 18-64 years of age with frequent institutional or occupational exposure to SARS-CoV-2. The Pfizer-BioNTech COVID-19 vaccine is authorized for use as a single heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. No COVID-19 vaccine is currently available for use in children 5-11 years of age.

Based on the considerations outlined above, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine under EUA for use as a 2-dose primary series (10 µg each dose, 3 weeks apart) in children 5-11 years of age.

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13 APPENDIX 1: C4591007 PHASE 1 (DOSE RANGING) – SUMMARY OF SAFETY AND IMMUNOGENICITY

During study C4591007 Phase 1, BNT162b2 was evaluated in U.S. children who were not at high risk of SARS-CoV-2 exposure, did not have medical conditions that represented risk factors for severe COVID-19, and did not have serologic/virologic evidence of SARS-CoV-2 infection. BNT162b2 dosages of 10 µg, 20 µg, then 30 µg were evaluated sequentially (n=16 participants per dosage) based upon the safety evaluation and recommendation by the internal review committee (IRC) to either advance to the subsequent dosage or terminate a specific dosage. Safety evaluation was the same as for Phase 2/3. SARS-CoV-2 50% neutralizing GMTs (SARS-CoV-2 mNG microneutralization assay) were assessed at 7 days after Dose 2.

Altogether, 48/49 (98%) of participants (assigned to the 10 µg, 20 µg, or 30 µg dosage groups combined) received two doses of BNT162b2 and completed the 1 month follow up visit after Dose 2. One BNT162b2 participant (20 µg dosage group) did not receive study vaccine. Following safety review of reactogenicity data from the initial 4 participants in the BNT162b2 30 µg dosage group, the IRC recommended to discontinue the 30 µg dosage, due to high frequencies of solicited ARs, and recommended that the remaining 12 participants receive the dosage selected for Phase 2/3 (i.e., 10 µg) at Dose 2. No participants from Phase 1 withdrew or discontinued from the study.

The frequencies of local and systemic adverse reactions were generally dose number and dosage dependent. Across dosages, systemic adverse reactions were generally mild and moderate in severity and resolved within 1 day of onset. No SAEs, deaths or AEs leading to withdrawal occurred at the time of data cut-off on July 16, 2021, with approximately 3 months of follow up. No participants reported anaphylaxis, myocarditis/pericarditis, or MIS-C. One BNT162b2 (30 µg) recipient reported Grade 1 axillary lymphadenopathy, which started 3 days after Dose 2 and resolved 17 days later; the AE was considered by the study investigator to be related to study intervention.

All four participants who received 30 µg for both doses developed mild-moderate redness and pain at the injection site, and 2 of the 4 participants developed swelling. In addition, all four subjects reported fevers to 38.9ºC with mild to moderate fatigue, and 2 of the 4 developed muscle pain of moderate severity following the second dose. One participant in the 20-µg group reported Grade 3 pyrexia (temperature to 39.7º C, also reported as a systemic adverse reaction, on Day 2 post-Dose 2), which resolved by Day 3. Both 10 and 20 µg dosages elicited similar

immune responses 7 days after Dose 2. In participants 5-11 years of age without evidence of SARS-CoV-2 infection up to 1 month post-Dose 2, the neutralizing antibody GMTs (NT50) at 1 month after Dose 2 were similar in the BNT162b2 10 µg and 20 µg groups (4163 and 4728, respectively).

The higher frequencies of solicited adverse reactions in participants receiving the 20 µg and 30 µg dosages, the favorable AE profile at the 10-µg dosage in participants 5-11 years of age followed for approximately 3 months after Dose 2, and the immunogenicity results demonstrating similar neutralizing antibody responses at the 10 and 20 µg dosages informed the IRC's decision to discontinue the 30-µg dosage and proceed to Phase 2/3 at the 10-µg dosage.

14 APPENDIX 2: COVID-19 AND SEVERE COVID-19 CASE DEFINITIONS

COVID-19

Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggered a potential COVID-19 illness visit:

- Fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea as defined by ≥3 loose stools/day, vomiting

Severe COVID-19

Confirmed COVID-19 plus at least one of the following symptoms:

- Clinical signs at rest indicative of severe systemic illness:
  - Respiratory rate and heart rate outside normal range
  - SpO2 ≤92% on room air, >50% FiO2 to maintain ≥92%, or PaO2/FiO2 <300 mm Hg
- Respiratory failure: defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO
- Evidence of shock or cardiac failure:
  - SBP (mm Hg); <70 + (age in years × 2) for age up to 10 years, <90 for age ≥10 years
  - Requiring vasoactive drugs to maintain blood pressure in the normal range
- Significant acute renal failure (serum creatinine ≥2 times ULN for age or 2-fold increase in baseline creatinine)
- Significant gastrointestinal/hepatic failure (total bilirubin ≥4 mg/dL or ALT 2 times ULN for age)
- Significant neurological dysfunction (Glasgow Coma Scale score ≤11, or acute change in mental status with a decrease in Glasgow Coma Scale score ≥3 points from abnormal baseline)
- ICU admission
- Death

Exhibit 6

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125742/0 **BLA APPROVAL**

BioNTech Manufacturing GmbH
Attention: Amit Patel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

August 23, 2021

Dear Mr. Patel:

Please refer to your Biologics License Application (BLA) submitted and received on May 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for COVID-19 Vaccine, mRNA.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2229 to BioNTech Manufacturing GmbH, Mainz, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, COVID-19 Vaccine, mRNA, which is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04368728 and NCT04380701.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture COVID-19 Vaccine, mRNA drug substance at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled and packaged at Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, Belgium and at Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo, Michigan. The diluent, 0.9% Sodium Chloride Injection, USP, will be manufactured at Hospira, Inc., (b) (4) and at Fresenius Kabi USA, LLC, (b) (4) .

You may label your product with the proprietary name, COMIRNATY, and market it in 2.0 mL glass vials, in packages of 25 and 195 vials.
We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for COVID-19 Vaccine, mRNA shall be 9 months from the date of manufacture when stored between -90ºC to -60ºC (-130ºF to -76ºF). The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) Following the final sterile filtration, (b) (4) , no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center

10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of COVID-19 Vaccine, mRNA, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 74, dated August 21, 2021, and the draft carton and container labels submitted under amendment 63, dated August 19, 2021.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on August 21, 2021. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on August 19, 2021, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125742 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports at monthly intervals as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages younger than 16 years for this application because this product is ready for approval for use in individuals 16 years of age and older, and the pediatric studies for younger ages have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

Submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.
Submit final study reports to this BLA STN BL 125742. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of an efficacy or a labeling

supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 16 through 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

4. Study C4591009, entitled “A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

5. Study C4591021, entitled “Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: January 31, 2022

   Study Completion: March 31, 2024

   Final Report Submission: September 30, 2024

7. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

8. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this assessment according to the following schedule:

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

9. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

Please submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125742. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of August 21, 2021 as outlined below:

10. Study C4591022, entitled “Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry.”

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

11. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age.

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

12. Study C4591012, entitled "Post-emergency Use Authorization Active Safety Surveillance Study Among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine."

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

13. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California."

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

Please submit clinical protocols to your IND 19736, and a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMC sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Study Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, PhD
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research